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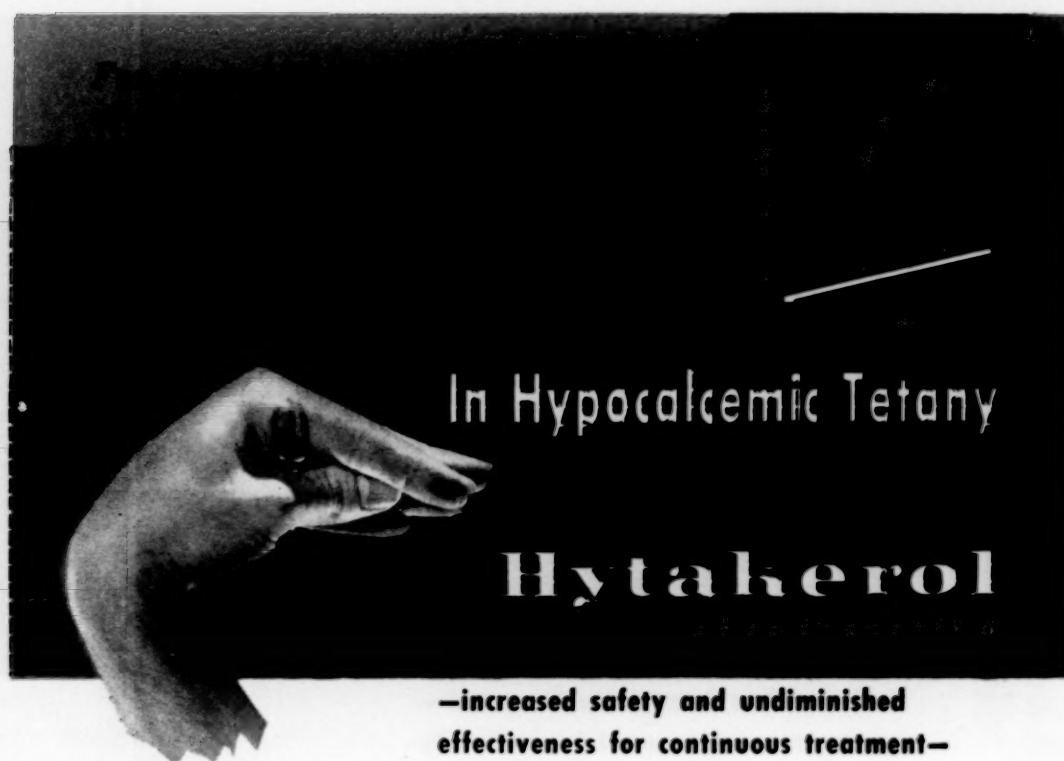
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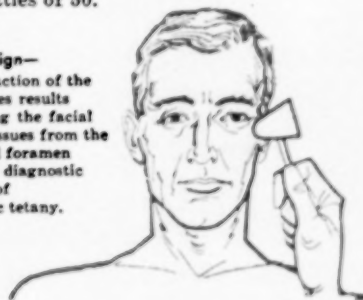
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1. Grollman, Arthur: Essentials of Endocrinology. Philadelphia, J.B. Lippincott Co., 2nd ed., 1947, p. 269.
2. Sandock, Isadore: Tetany and ovarian function. J.A.M.A., 160:659, Feb. 25, 1956.

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Tonic contraction of the facial muscles results from tapping the facial nerve as it issues from the stylomastoid foramen—one of the diagnostic indications of hypocalcemic tetany.



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The American Journal of Medicine

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Clinical Studies

- Multiple Myeloma and the Adult Fanconi Syndrome. I. Report of a Case with Crystal-like Deposits in the Tumor Cells and in the Epithelial Cells of the Kidney
RALPH L. ENGLE, JR. AND LILA A. WALLIS 5

- The Adult Fanconi Syndrome. II. Review of Eighteen Cases
LILA A. WALLIS AND RALPH L. ENGLE, JR. 13

The first paper describes a patient who had proved multiple myeloma and also the adult form of the Fanconi syndrome. The authors suggest that the Fanconi syndrome was due to damage to the proximal convoluted tubules, in which crystals were found (presumably a crystalline protein), postulated to be reabsorbed Bence Jones protein. If Fanconi syndrome occurs as a complication of multiple myeloma, it must be a rare complication indeed. The second paper develops the concept of secondary Fanconi syndrome further by bringing together evidence from many sources that proximal tubular damage, notably by a variety of heavy metals, may so reduce the Tm for many metabolites as to produce all the characteristics of the Fanconi syndrome. It is important that this state be recognized since the resulting deficiencies are amenable to effective replacement therapy.

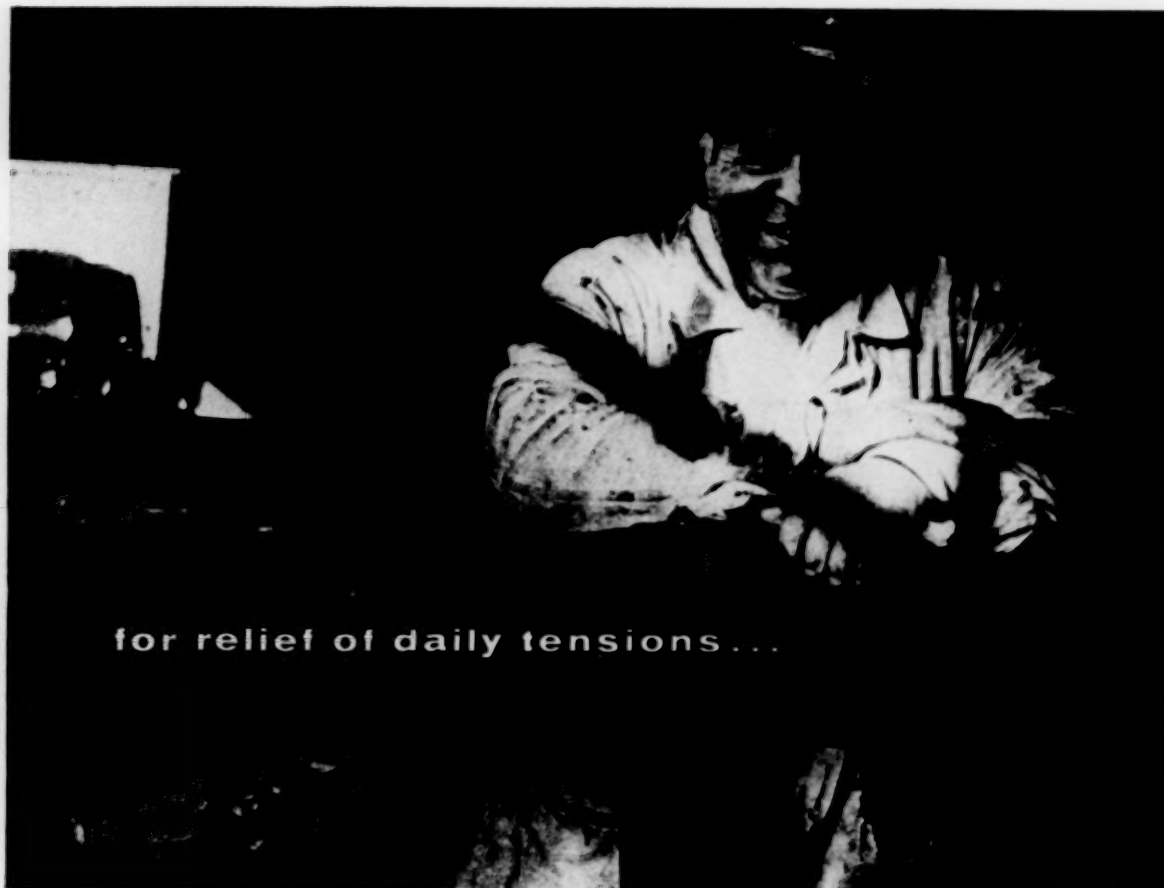
- Glycoproteins in Serum from Patients with Myeloma, Macroglobulinemia and Related Conditions . . . C.-B. LAURELL, H. LAURELL AND J. WALDENSTRÖM 24

Increasing interest in the macroglobulinemias has been accompanied by many frustrations in diagnosis because of the non-specificity of the "typical" clinical picture and the need of ultracentrifugal analysis of the serum proteins to establish the presence of components of very high molecular weight. Some simpler and more generally accessible laboratory method of diagnosis would be welcome. In this study a comparison is made of the polysaccharide content of abnormal serum protein components in multiple myeloma and in macroglobulinemia. It would appear that, in confirmation of previous investigators, the abnormal serum protein components in the macroglobulinemias generally contain more carbohydrate than the abnormal components in myeloma. The distinction involves paper electrophoresis and appropriate staining techniques.

- Pulmonary Disease Following Chronic Chemical Ganglionic Blockade. A Clinical and Pathologic Study
H. MITCHELL PERRY, JR., ROBERT M. O'NEAL AND WILBUR A. THOMAS 37

In a report of unusual intrinsic as well as therapeutic interest, the authors describe the development of fibrinous pneumonitis in the course of protracted treatment of eight hypertensive patients

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*Ferguson, J. T.: J. Am. Geriatrics Soc. 4:1080, 1956.



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NUMBER ONE

with methonium salts plus hydralazine. The most striking clinical manifestation of this disorder, apparently induced in conjunction with prolonged ganglionic blockade by the antihypertensive agents employed, is marked tachypnea, probably the expression of alveolar-capillary block. The anatomic changes found in the lungs at necropsy resemble those of "uremic pneumonia" but the patients in question presented only moderate nitrogen retention. The interesting suggestion is made that, at least in respect to the pathogenesis of fibrinous pneumonitis, methonium salts may exert effects similar to those of certain unidentified nitrogen retention products of the uremic state.

Clinical Determination of the Diffusion Capacity of the Lungs. Comparison of Methods in Normal Subjects and Patients with "Alveolar-Capillary Block" Syndrome

ASHER MARKS, DAVID W. CUGELL, JOHN B. CADIGAN AND
EDWARD A. GAENSLER

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Recent clarification of the alveolar-capillary block syndrome has emphasized the need for an accurate and simple method for determining the diffusing capacity of the lungs, especially since an increasing number of patients are seen with dyspnea or pulmonary insufficiency out of proportion to any measured ventilatory defect. This thorough study of three methods for the determination of the diffusing capacity, i.e. the two-level O₂ method, the steady state CO method and the single breath CO method, revealed that the first two give correlative values. The third method, although simple to perform, gives values which are much higher than the other two. A high result by this method therefore does not rule out a diffusion abnormality but a low value is significant and may be useful as a screening test.

Effects of Venesection on Pulmonary and Cardiac Function in Patients with Chronic Pulmonary Emphysema and Secondary Polycythemia

J. HOWLAND AUCHINCLOSS, JR. AND JOHN J. DUGGAN

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The place of phlebotomy in the management of patients with chronic pulmonary emphysema and secondary polycythemia, particularly when associated with cor pulmonale and right heart failure, is still controversial. It would seem that the most convincing way to settle the matter would be to test the response to venesection in terms of indexes of pulmonary and cardiac function. Interpretations of such results vary, however, and the results of the present study also are subject to variable interpretation. It is made clear, nevertheless, that the benefits of venesection alone are negligible from the long term point of view. Certain immediate advantages may accrue, however, notably a transitory reduction in pulmonary artery pressure and rise in arterial oxygen saturation, albeit at the cost of a fall in cardiac output.

Hydrothorax in Congestive Heart Failure

GEORGE A. RACE, CHARLES H. SCHEIFLEY AND JESSE E. EDWARDS

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The not too infrequent occurrence of unilateral left-sided pleural effusion in patients with or without congestive failure seems invariably to set off a long train of confused speculation to account for what has come to be regarded as a paradoxical phenomenon quite distinct in etiology from unilateral right-sided pleural effusion. The present study, which to be sure is highly selective in dealing only

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with fatalities, tends to negate this impression, indicating that in congestive failure the prevalence of unilateral effusion on one or the other side is not so different as to necessitate the assumption of wholly distinct causal mechanisms. This may be one reason why the proposed explanations of the presumed differences, which are here reviewed, are so controversial.

- The C-Reactive Protein Determination as an Index of Myocardial Necrosis in Coronary Artery Disease . . . IRVING G. KROOP AND NATHAN H. SHACKMAN 90

The C-reactive protein test is a sensitive but quite non-specific indicator of the presence of infection, tissue necrosis or neoplasm. It is here employed as an accessory to the usual criteria for the diagnosis or exclusion of myocardial necrosis in patients with precordial pain. The results described indicate that the test is negative in the "premonitory" preinfarction phase of acute myocardial infarction, positive in the presence of classic electrocardiographic evidences of acute "transmural" infarction, negative in coronary insufficiency without acute myocardial necrosis, and positive when various complications arise, sometimes even when the erythrocyte sedimentation rate and other screening tests fail. Despite the fallibility of the C-reactive protein test by reason of its non-specificity, it may have a place of limited usefulness in this connection, and deserves further exploration.

- Hypochromic Anemia with Hyperferricemia Responding to Oral Crude Liver Extract
DANIEL L. HERRIGAN, RICHARD M. WHITTINGTON, RUSSELL WEISMAN, JR.
AND JOHN W. HARRIS 99

Two unusual cases of hypochromic anemia, one with pigment cirrhosis of the liver, are presented. The anemia was characterized by hypochromia, morphologic abnormalities of the erythrocytes and bone marrow evidence of erythroid maturation arrest. Serum-iron levels were high, with increased saturation of iron binding capacity. There was little response to iron, vitamin B₁₂, folic acid or leucovorin but a crude liver preparation proved to be effective. The implication is that the patients described reflect failure to utilize iron for synthesis of hemoglobin due to deficiency of a substance not supplied by iron, refined liver extracts, folic acid or leucovorin but present in crude liver extract.

Review

- Agnogenic Myeloid Metaplasia. Its Natural History and Present Day Management
JAMES W. LINMAN AND FRANK H. BETHELL 107

This is a timely and welcome review of current concepts concerning a not infrequent disorder which has been the subject of much confusion and controversy. The authors base their views upon a solid experience of fifty-six cases which are analyzed with circumspection. They conclude that agnogenic myeloid metaplasia, whatever its antecedent or terminal aspects, is a disease *sui generis*, distinct from leukemia, and "most likely a manifestation of a myeloproliferative process involving all elements, both hemic and stromal, which develop from the myeloid reticulum" in response to an unidentified stimulus. They describe the characteristic clinical course and the anomalies in blood cell morphology, emphasizing the prevalence of peripheral erythrocyte malformation and thrombocytosis and discounting the increase in immature granulocytes. Problems of management, in particular the disputed place of splenectomy, are discussed rationally.

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Seminar on Bone Diseases

Emerging Concepts of the Structure and Metabolic Functions of Bone

W. F. NEUMAN AND M. W. NEUMAN 123

This lively presentation offers the Neumans' current views (subject, as they indicate, to change without notice) on the chemistry and ultrastructure of bone, and the physiologic aspects of bone formation and mobilization. Substantial progress has been made in elucidating the composition and surface chemistry of bone, to which the Neumans have themselves made important contributions, referred to here. The mechanisms of calcification of cartilage, of bone formation, of maintenance of the steady state of bone metabolism, and of mobilization of bone remain obscure, however, and the scanty available facts must, for the present, be pieced out with speculations.

Clinico-pathologic Conference

Dyspnea, Weakness and Ocular Pain 132

Clinico-pathologic Conference (Washington University School of Medicine).

Case Reports

Idiopathic Endomyocardial Necrosis GRANT N. STEMMERMANN 142

Dr. Stemmermann has some unorthodox speculations about the pathogenesis of idiopathic endomyocardial necrosis in general and, in particular, the association with pancreatitis noted in the case described.

Occluding Thrombus of the Right Atrium. Intermittent Tricuspid Occlusion in a Case of Atrial Infarction with Mural Thrombosis

E. D. PELLEGRINO, E. V. OLMSTEAD AND G. B. TOMPKINS 151

An interesting case of intermittent tricuspid valve occlusion by a large mural thrombus implanted upon the site of an atrial infarct.

Salt-losing Nephritis with Fixed Urinary Composition

HARVEY C. KNOWLES, JR., HOWARD LEVITIN AND ALBERT BRIDGES 158

This is an interesting report of a patient with presumed pyelonephritis and excretion of urine of relatively fixed composition involving excessive loss of sodium. Relatively high sodium intake was required for prevention of symptoms of sodium depletion. The authors lean to the concept of tubular excretion of some water and sodium, with impairment of this mechanism to explain the findings in this case.

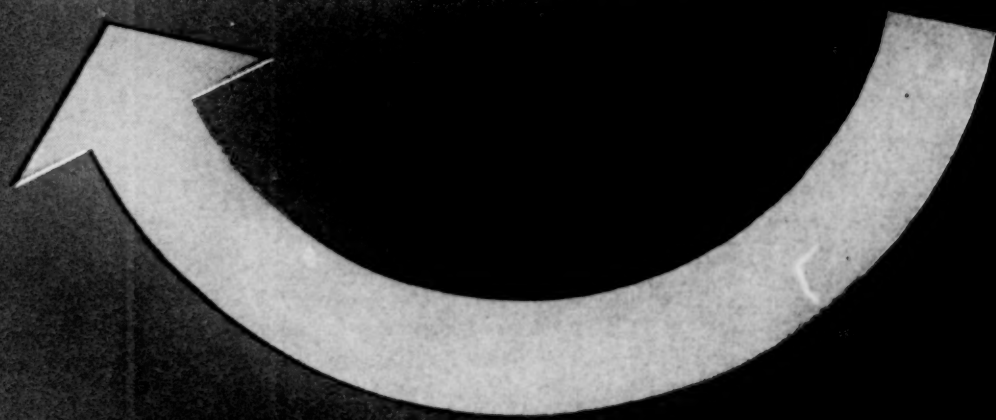
Observations Concerning the Origin of Shock Associated with Acute Cor Pulmonale

ARTHUR SELZER AND HERBERT W. BRADLEY 163

The authors had an unusual opportunity to study the sequence of hemodynamic events accompanying the development of shock due to pulmonary embolism and acute cor pulmonale. Their findings clarify the mechanisms of "cardiogenic" shock.

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Lesions Resembling Vitamin B Complex Deficiency and Urinary Loss of Zinc Produced by Ethylenediamine Tetra-acetate

H. MITCHELL PERRY, JR. AND HENRY A. SCHROEDER 168

The authors describe some unusually intriguing observations made in the course of protracted administration of the chelating agent, EDTA, in a patient with amyloid nephrosis. These include lowering of the serum cholesterol, development of mucocutaneous lesions resembling acute avitaminosis B and an outpouring of zinc in the urine as the result, presumably, of chelation. The last two phenomena might be causally related.

Metal Fume Fever A. IRVING SWILLER AND HELEN EMMER SWILLER 173

As the authors point out, more general information about the acute illness caused by exposure to zinc fumes would be beneficial to physician and patient alike.

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^{*}Campbell, D. G., in Wohl, M. G., & Goodhart, R. S., *Modern Nutrition in Health and Disease*, Philadelphia, Lea and Febiger, 1955, p. 835.

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<i>Johns Hopkins Hospital</i>
Baltimore 5, Md. |
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Dr. D. HAROLD COPP
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| 3. March—Pathology of Bone Disease
Dr. RICHARD H. FOLLIS, JR.
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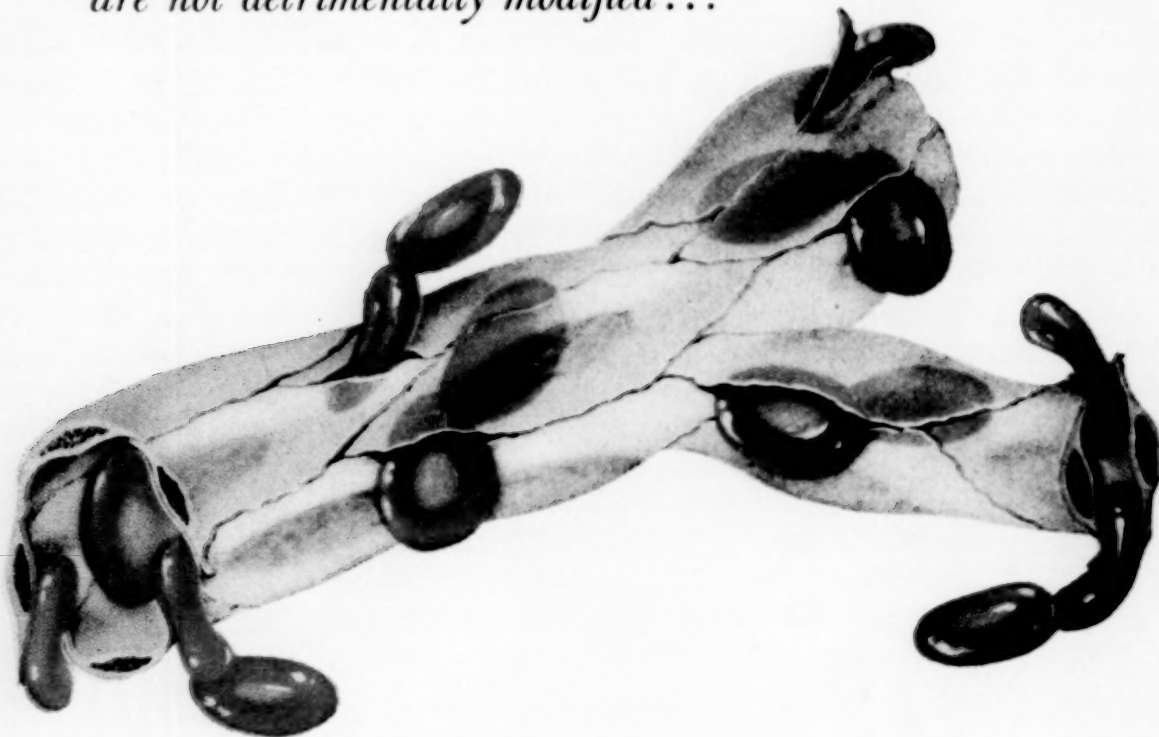
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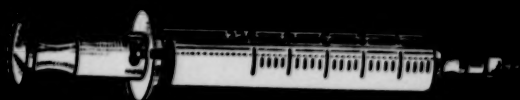
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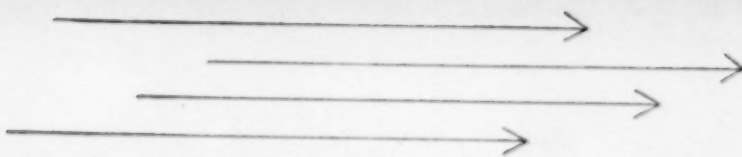
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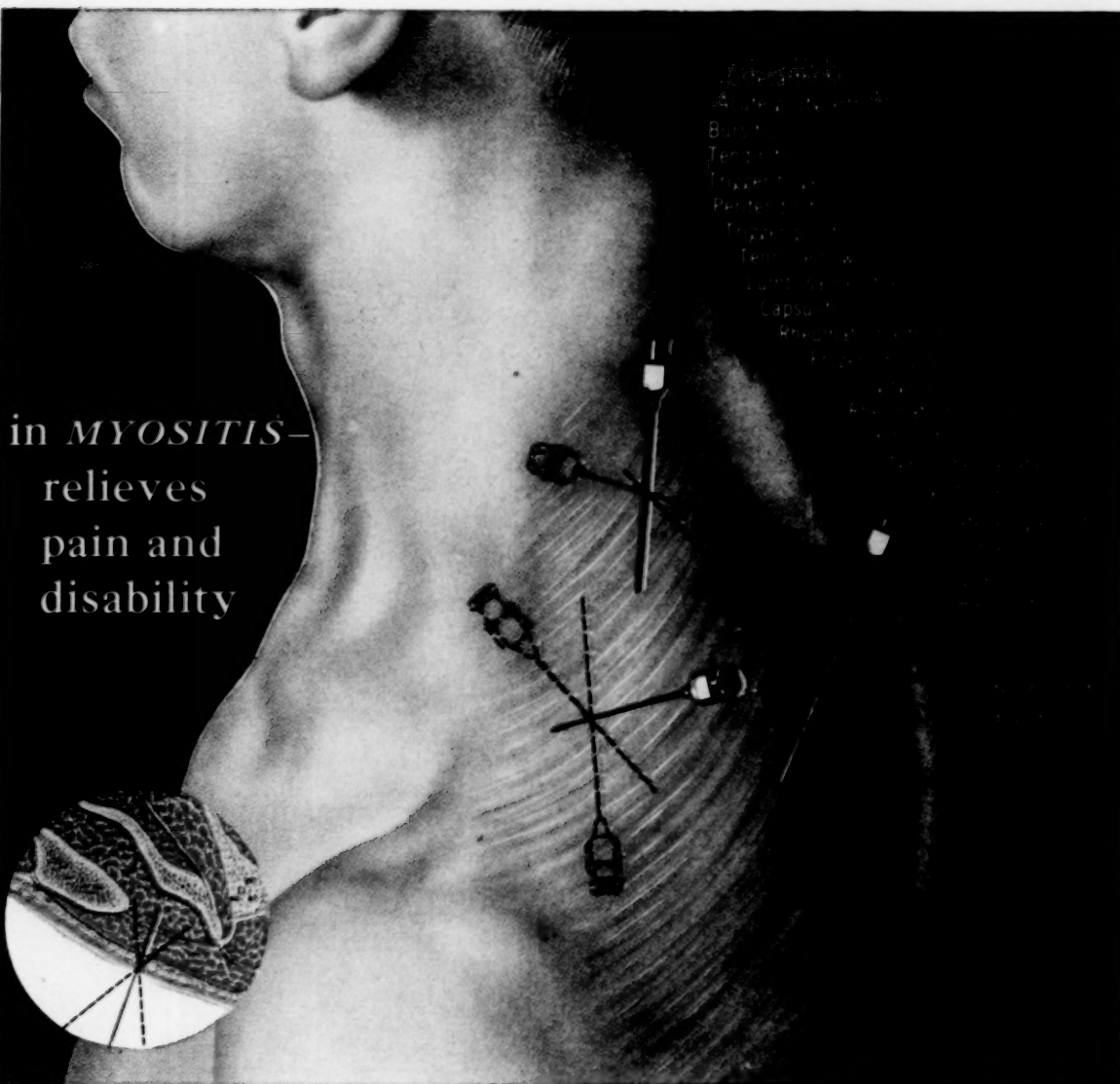
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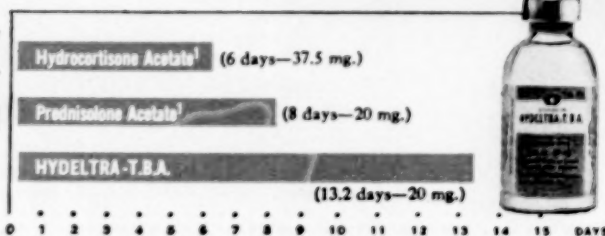
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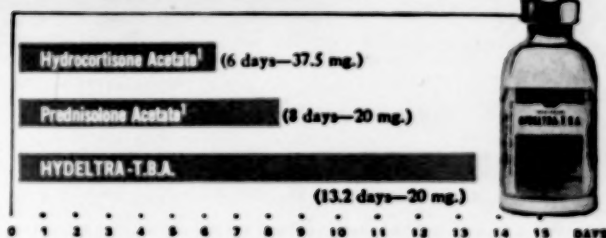
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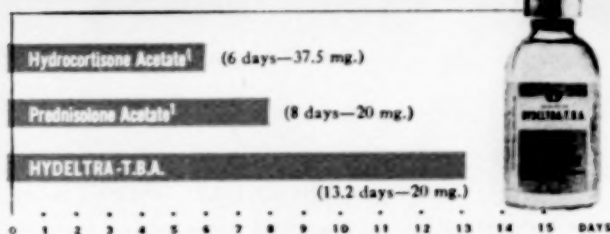
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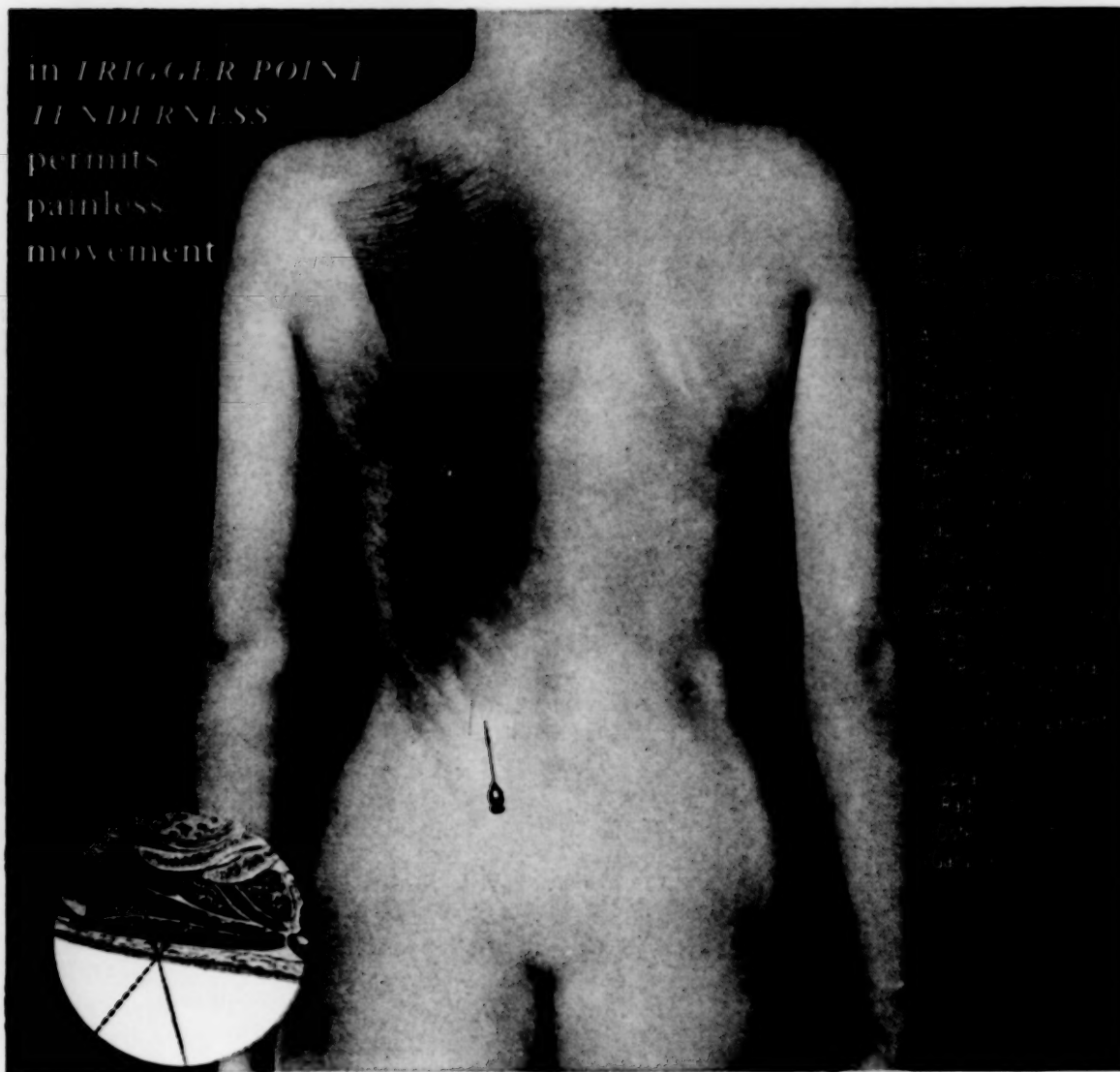
1. Hollander, J. L., Paper read at conference in New York City, May 31 and June 1, 1955

NEW HYDELTRA®-T.B.A.

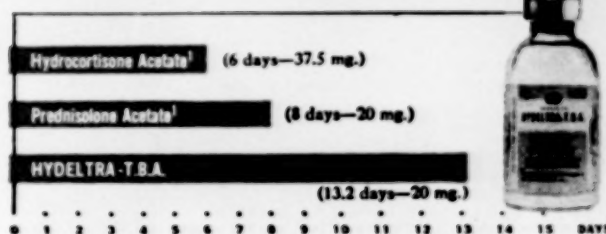
(Prednisolone tertiary-butylacetate, Merck)

for relief that lasts—longer

in TRIGGER POINT
TENDERNESS
permits
painless
movement



Duration of relief
exceeds that
provided by any
other steroid
ester



Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone tertiary-butylacetate, in 5-cc. vials.



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¹ I. Hollander, J. L., Paper read at conference in New York City, May 31 and June 1, 1955

NEW HYDELTRA®-T.B.A.

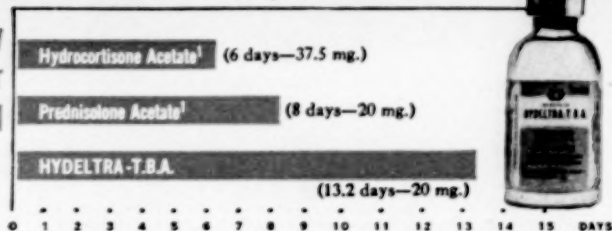
(Prednisolone tertiary-butylacetate, Merck)

for relief that lasts—longer

in *SPRAINS*—
reduces tenderness,
swelling and
limitation of motion



Anti-inflammatory
effect lasts longer
than that provided
by any other
steroid ester



Dosage: the usual intra-articular, intra-bursal or soft tissue dose ranges from 20 to 30 mg. depending on location and extent of pathology.

Supplied: Suspension 'HYDELTRA'-T.B.A.—20 mg./cc. of prednisolone tertiary-butylacetate, in 5-cc. vials.



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In Angina Pectoris

*when every
moment counts*

Relief in 10 to 30 Seconds

Medihaler Nitro the Unique Measured Dose Inhalation Principle

- More rapid relief than from sublingual nitroglycerin because pulmonary portal of entry affords most direct route . . . only the single-cell barrier of alveolar lining to cross.
- Each measured dose of Medihaler-Nitro delivers 0.25 mg. of octyl nitrite, equivalent in vasodilating action to 1/100 gr. nitroglycerin.
- In contrast to amyl nitrite, Medihaler-Nitro has no irritating odor . . . is virtually free from side actions . . . and vasodilating effect lasts longer.
- Medication and Adapter fit into neat plastic case, convenient for pocket or purse.
- Economical . . . each 10 cc. bottle delivers 200 metered doses . . . no deterioration with age.

Note: First prescription should include medication and Medihaler Oral Adapter.



Pentoxylon®

Reduces incidence and severity of anginal attacks. Each long-acting tablet contains pentaerythritol tetranitrate (PETN) 10 mg. and Rauwiloid® (alseroxylon) 1 mg. Patients on Pentoxylon suffer fewer anginal attacks.

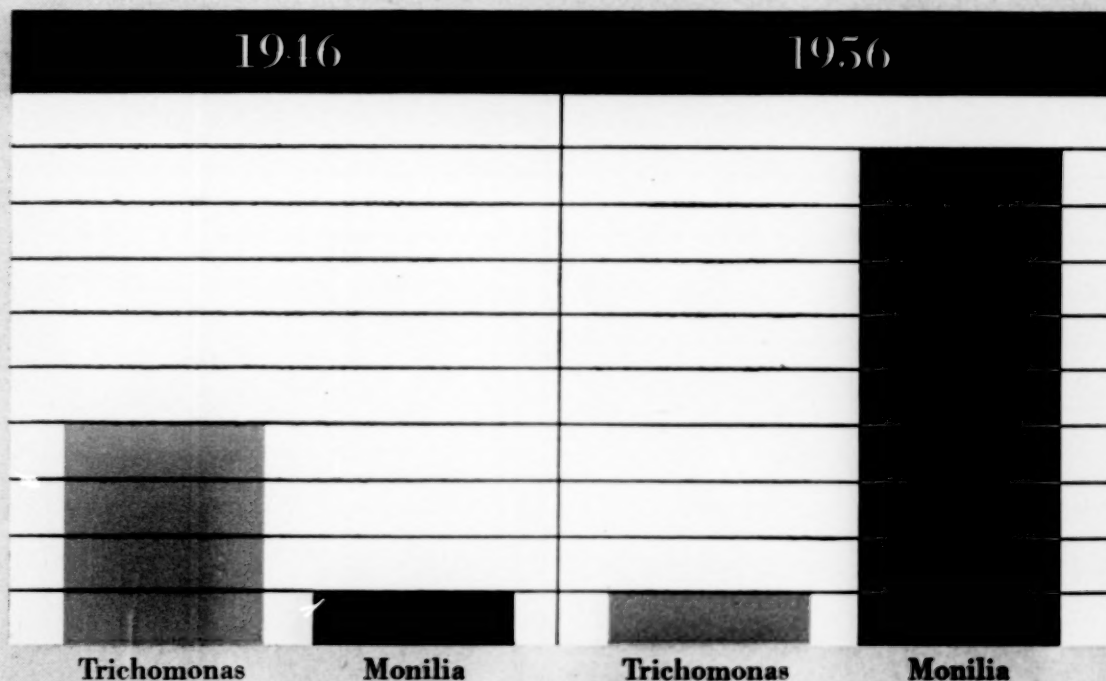
Riker

LOS ANGELES

AN IMPORTANT CLINICAL CONSIDERATION:

the rising incidence of moniliasis since the introduction of broad spectrum antibiotics

EXAMPLE: *Candida albicans* (monilia) as a cause of vaginitis^{1,2}



The use of *any* antibiotic may cause the troublesome and potentially serious complication of monilial superinfection by suppressing the bacterial flora of the intestinal tract and allowing monilia to proliferate.

"Even one day of therapy may be sufficient to provoke an unfavorable chain of events and this fact should be kept in mind whenever a patient is to receive an oral antibiotic for even a minimal period of time."³

Mysteclin provides
intestinal and genital
same time protection
with the use of

References:

1. Lee, A. E. *et al.* *JAMA* 159:1227, 1954.
2. *JAMA* 159:1227, 1954.
3. Paper presented at the
Meeting, Washington, D.C.

MYSTECLIN IS PARTICULARLY INDICATED IN:

*the only broad spectrum antibiotic preparation with added
protection against monilial superinfection*

Mysteclin

Erythromycin in Treating Pneumonia

A 27-year-old man, a chronic alcoholic, was admitted with a history of an alcoholic spree followed by a cough, greenish sputum and chills and fever.

Physical examination showed a temperature of 104 F. and indicated pneumonia in the right lower lobe. This was confirmed by X-ray. The sputum revealed gram-positive diplococci and blood culture subsequently grew Type VII pneumococci.

The patient was treated with erythromycin, 300 mg. every six hours per os. His temperature dropped to normal by 48 hours and X-ray of the chest revealed considerable clearing by the fourth hospital day. After 10 days hospitalization, the patient was fit for discharge.¹

At the First Antibiotics Symposium, we reported the successful treatment with erythromycin of *H. influenzae* pneumonia and bacteremia. A second patient with *H. influenzae* pneumonia and bacteremia had a clinical course almost identical to the one previously reported, with cure obtained by treatment with 500 mg. of erythromycin per os every four hours for 14 days.

Of these 132 patients with bacterial pneumonia, 127 (96%) had a good clinical result. One patient with lobar pneumonia had a good initial response but had delayed resolution after treatment.

"Highly Effective in Pneumonia"

In one investigation, 75 adult patients with bacterial pneumonia were treated with erythromycin. In his summary, the clinician reported: "It is concluded that erythromycin is highly effective in the treatment of pneumonia due to gram-positive bacteria."²

This, of course, is only one of many reports showing the effectiveness of ERYTHROCIN against coccic infections. You'll get the same good results (nearly 100% in common, bacterial respiratory infections) when you prescribe ERYTHROCIN. **Abbott**



Erythrocin[®]

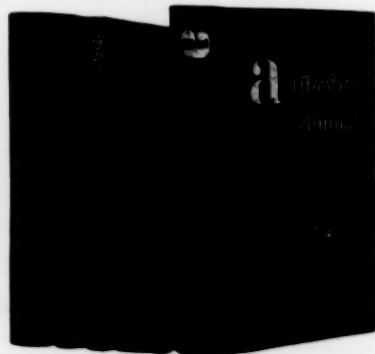
(Erythromycin, Abbott)

STEARATE

"No Serious Side Effects Occurred"

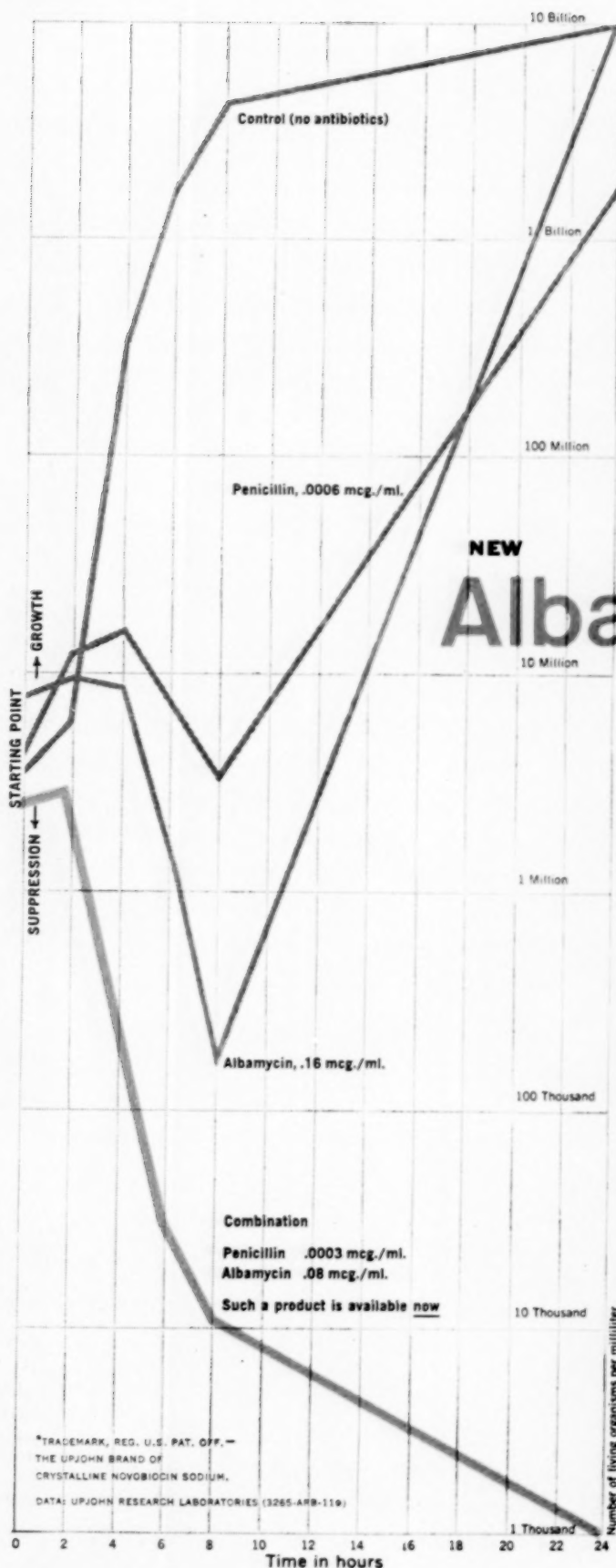
After a study of 171 patients treated with erythromycin, the investigator wrote: "No serious side effects occurred with prolonged therapy or with doses up to 8 Gm. per day in the severe infections."¹

Actually, ERYTHROCIN stands on a remarkable record of safety. After four years, there's not a single report of a severe or fatal reaction attributable to erythromycin. In addition, you'll find allergic manifestations rarely occur. *Filmtub* ERYTHROCIN Stearate (100 and 250 mg.), in bottles of 25 and 100. **Abbott**



® Filmtab—Film-Sealed tablets, Abbott; pat. applied for.

1. Romansky, M.J., et al., *Antibiotics Annual* 1955-1956, p. 48.
2. Waddington, W. S., Maple, F. C., and Kirby, W. M. M., *A.M.A. Archives of Internal Medicine*, 1954, p. 556.



average dosage only t.i.d.

antibiotic synergism

The three gray lines of this graph show the growth rate of a penicillin-sensitive strain of *Staphylococcus* (*Micrococcus pyogenes*, var. *aureus*) under 3 conditions:

1. In the absence of antibiotics
2. In the presence of subinhibitory concentration of penicillin
3. In the presence of subinhibitory concentration of Albamycin*

Even half these subinhibitory concentrations of penicillin and Albamycin, when combined, (black line) produce a dramatic bactericidal effect.

NEW Alba-Penicillin*

(Albamycin plus penicillin)

Compare it with
the antibiotic you are
currently using:

Range of effectiveness: Alba-Penicillin is effective against the organisms that cause the overwhelming majority of bacterial infections (*Staphylococci*, *Streptococci*, *Pneumococci*, *Proteus*).

Risk of resistance: Because in vitro tests show this combination is synergistic against even *Staphylococci* already resistant to all other antibiotics, the risk of resistance is minimized.

Risk of enterocolitis: Because it has little or no effect on the predominant Gram-negative intestinal bacteria, and is highly effective against *Staphylococci*, there is virtually no danger of enterocolitis due to alteration in intestinal flora, or of other side effects such as perianal pruritus.

Convenience: Alba-Penicillin is oral therapy, and the average adult dosage is only 1 to 2 capsules t.i.d., which eliminates middle-of-the-night medication.

It is available in bottles of 16 capsules. Each capsule contains 250 mg. Albamycin (as novobiocin sodium, crystalline) and 250,000 units penicillin G potassium.

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increasingly preferred
by physicians
strikingly effective
for patients

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(PREDNISONE)

excellent relief of pain, swelling, tenderness; diminishes joint stiffness—
facilitates early physical therapy—
expedites rehabilitation

dietary regulations usually unnecessary

minimizes incidence of electrolyte imbalance

1, 2.5 and 5 mg. tablets

METICORTEN,^{*} brand of prednisone.

^{*}T. M.

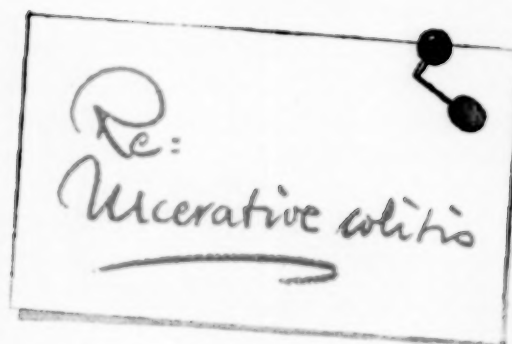
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4%



This is "the most valuable drug that has been introduced for the treatment of ulcerative colitis" in recent years.¹ Results of treatment with Azulfidine "far exceed those of any previous drug used".² "It has been effective in controlling the disease in approximately two-thirds of patients who had previously failed to respond to standard colitis therapy currently in use."³

1. BARGEN, J. A.: "Present Status of Hormonal and Drug Therapy of Ulcerative Colitis", *South. M. J.* 48: 192 (Feb.) 1955.
2. BARGEN, J. A. and KENNEDY, R. L. J.: "Chronic Ulcerative Colitis in Children", *Postgrad. Med.* 17: 127 (Feb.) 1955.
3. MORRISON, L. M.: "Response of Ulcerative Colitis to Therapy with Salicylazosulfapyridine", *J. A. M. A.* 151: 366 (Jan. 31) 1953.



Azulfidine
BRAND OF SALICYLAZOSULFAPYRIDINE

PHARMACIA LABORATORIES, INC.
270 Park Avenue, New York 17, N.Y.

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BIOPAR® FORTÉ

T A B L E T S

*containing non-inhibitory intrinsic factor
providing "parenteral B₁₂ therapy" in a tablet*



*2 tablets a day provide the same rapid and intense
hemopoietic response as that obtained from injectable B₁₂*

Biopar Forté, a new development in oral vitamin B₁₂ therapy, contains non-inhibitory intrinsic factor superior to the ordinary factor preparations. The non-inhibitory factor permits optimal absorption of vitamin B₁₂ at therapeutic dosage levels. Thus, stated potency and actual hemopoietic potency are more nearly equal than in vitamin B₁₂ products containing the ordinary intrinsic factor.

Biopar Forté is also useful as an aid to nutrition, appetite, growth and convalescence; to correct deficient intestinal absorption of vitamin B₁₂ particularly in elderly patients; and to relieve minor muscle and nerve pains, especially of neuritic origin.

Each Biopar Forté tablet contains:
Vitamin B₁₂ with Intrinsic Factor Concentrate (non-inhibitory) ½ U.S.P. Unit (Oral)*
Vitamin B₁₂ (activity equivalent) 25 mcg.

Supply: Bottles of 30 tablets

Attention: Store in a cool place

*Unitage established prior to compounding

**THE ARMOUR LABORATORIES**

A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

Even stubborn
trichomoniasis yields...
because Tricofuron
is effective
during menstruation,
the critical time
for therapy.



TRICOFURON®

Recurrences of trichomoniasis "are most likely to follow the menstrual period."¹

"Over and over again today patients are seen with what is said to be an intractable, treatment-resistant *Trichomonas* infestation, but history-taking often reveals that such patients have never had treatment prescribed during any menstrual period."²

Menstrual blood in the vagina "forms an excellent medium for the rapid multiplication of *T. vaginalis*"³ and "lowers the acidity of the vagina and hence there is a tendency to recrudescence [of trichomoniasis] at that time."⁴

Tricofuron is powerfully trichomonocidal "even in the presence of vaginal debris and menstrual blood."⁵

For 44 of 48 patients: lasting cure was obtained with a single course of Tricofuron therapy.⁵

Vaginal Suppositories—for home use—each morning and night through one cycle, including the important menstrual days. Contain 0.25% Furoxone* (brand of furazolidone) in a water-miscible base. Box of 12, each sealed in green foil.

Vaginal Powder—for office use—applied by the physician at least once a week, except during menstruation. Contains 0.1% Furoxone in an acidic powder base of lactose, dextrose, citric acid and a silicate. Bottle of 30 Gm.

References: 1. Bernstine, J. B., and Rakoff, A. E.: *Vaginal Infections, Infestations and Discharges*, New York, The Blakiston Company, Inc., 1953, p. 235. 2. Overstreet, E. W.: *Arizona M.* **10**:383, 1953. 3. Schwartz, J.: *Obst. Gyn.*, N. Y. **7**:312, 1956. 4. Crossen, R. J.: *Diseases of Women*, St. Louis, The C. V. Mosby Company, 1953, p. 292.

EATON LABORATORIES



NORWICH, NEW YORK

Nitrofurans—a new class of antimicrobials—neither antibiotics nor sulfonamides

THE CASE FOR EARLY CONTROL OF HYPERTENSION¹

In the Guest Editorial for GP in July, Dr. Edward D. Freis reexamines two major questions:

1. Should Hypertension Be Treated Early? Freis finds the case for early treatment to rest on cause-and-effect evidence: "... high pressure, ... and *nothing else but this high pressure*, creates many if not all the organic manifestations that lead to the final disability and eventual death of the patient." The "evidence presents a cogent argument for the treatment of hypertension early before vascular damage has occurred."¹

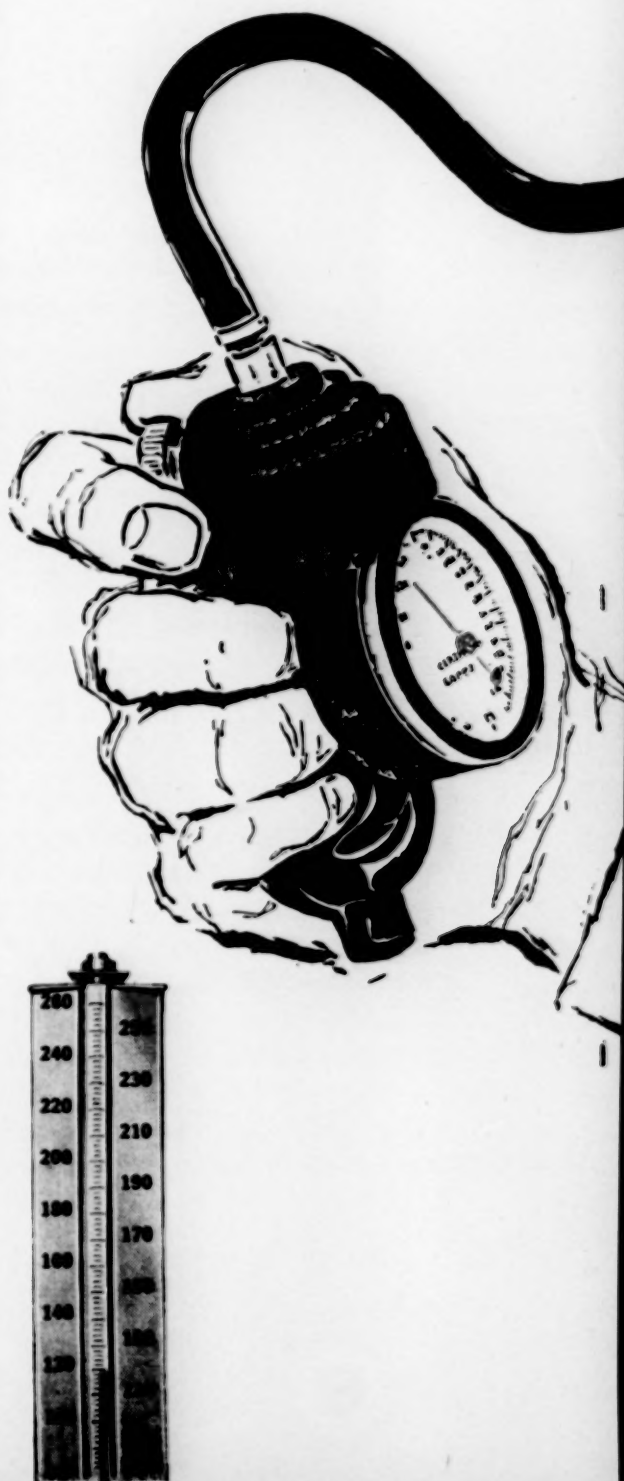
2. What is the Role of the More Potent Agents? "... the evidence ... suggests that the technique [for the effective and safe use of such agents as ANSOLYSEN] should be more widely learned and employed. Furthermore, ... the patients with early hypertension, especially those without renal damage, are far more easily controlled, with fewer side effects, than the patients with advanced hypertension."¹

Freis cautions that these views are not presented as dogma; "... they have been developed to show the other side of an argument that seems to have many points in its favor."¹

1. Freis, Edward D.: Guest Editorial. GP 14:72 (July) 1956.

ANSOLYSEN[®]
TARTRATE Pentolinium Tartrate
Lowers Blood Pressure

Wyeth
Philadelphia 1, Pa.



Medihaler

Means self-powered, uniform, measured-dose inhalation therapy... made possible by specially designed metered-dose valve...



Medihaler

Means notably safe and effective therapy when indicated for children. Medication is in leak-proof plastic coated bottles...



Medihaler

Means true nebulization. Each measured dose provides 80 per cent of its particles in the optimal size range—0.5 to 4 microns radius—insuring effective penetration of the respiratory tract.



Medihaler

Medication and Adapter fit into neat plastic case, convenient for pocket or purse...

Medihaler

Means an unbreakable Oral Adapter—no movable parts—no glass to break—no rubber to deteriorate...



Medihaler

Means greater economy—no costly glass nebulizers to replace, and one or two inhalations usually suffices for prompt relief.



The Unique Measured-Dose Inhalation Method

In Asthma

For Rapid Relief of Acute or Continuing Bronchospasm

Medihaler-EpiTM

Riker brand of epinephrine 0.5% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.125 mg. epinephrine. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Medihaler-Epi replaces injected epinephrine in emergency situations in which respirations have not ceased. It provides rapid relief in acute food, drug, or pollen reactions (including urticaria, bronchospasm, angioneurotic edema, edema of glottis, etc.). In most instances only one inhalation is necessary.

Medihaler-IsoTM

Riker brand of isoproterenol HCl 0.25% solution in inert, nontoxic aerosol vehicle. Each ejection delivers 0.06 mg. isoproterenol. In 10 cc. vial with metered-dose valve, sufficient for 200 inhalations.

Note: First prescription for Medihaler medications should include the desired medication and Medihaler Oral Adapter.

*Rx Medihaler-Iso
and
Medihaler Oral
Adapter*

Riker

NEW

Rheumatoid Arthritis

Ataraxoid*





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'Roche'

For round-the-clock therapy

With two doses a day

Lipo Gantrisin 'Roche'—a new, palatable liquid for antibacterial therapy—offers three significant features:

1. Only two doses a day needed in most cases
2. Adequate twelve-hour blood levels after a single dose
3. Same therapeutic advantages as Gantrisin 'Roche'

Lipo Gantrisin® Acetyl—brand of acetyl sulfisoxazole in vegetable oil emulsion



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aging complex
now

promotes vigor
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mineral-vitamin-hormone supplement

favorably alters concomitants of aging

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Kapseals®

comprehensive physiologic supplement



each Kapseal contains:

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Vitamin A	1,667 Units (0.5 mg.)
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Ascorbic acid	33.3 mg.
Nicotinamide	16.7 mg.
Vitamin B ₂	0.67 mg.
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Folic acid	0.1 mg.
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Ferrous sulfate (exsiccated)	16.7 mg.
Iodine (as potassium iodide)	0.05 mg.
Calcium carbonate	66.7 mg.

DIGESTIVE ENZYMES

Taka-Diastase®	20 mg.
Pancreatin	133.3 mg.

PROTEIN IMPROVEMENT FACTORS

L-Lysine monohydrochloride	66.7 mg.
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GONADAL HORMONES

Methyl testosterone	1.67 mg.
Theelin.	0.167 mg.

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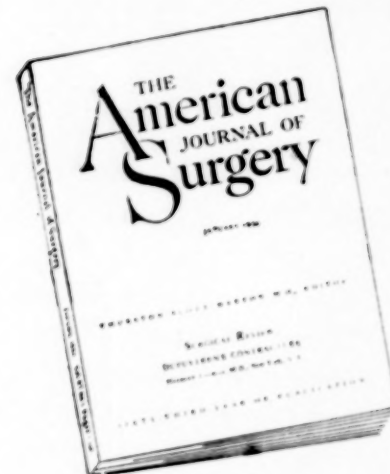
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Female patients should follow each 21-day course with a 7-day rest interval.

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For the first time in the treatment of depression, improvement in mentation *and* metabolism *and* mood is now possible with a single therapy—**Dexazyme**.

Dexazyme elevates mood by combining low, *safer* dosages of dextro-amphetamine with Pentrazol.*

Dexazyme improves mentation and clarity of consciousness through action of Pentrazol *and* niacin.

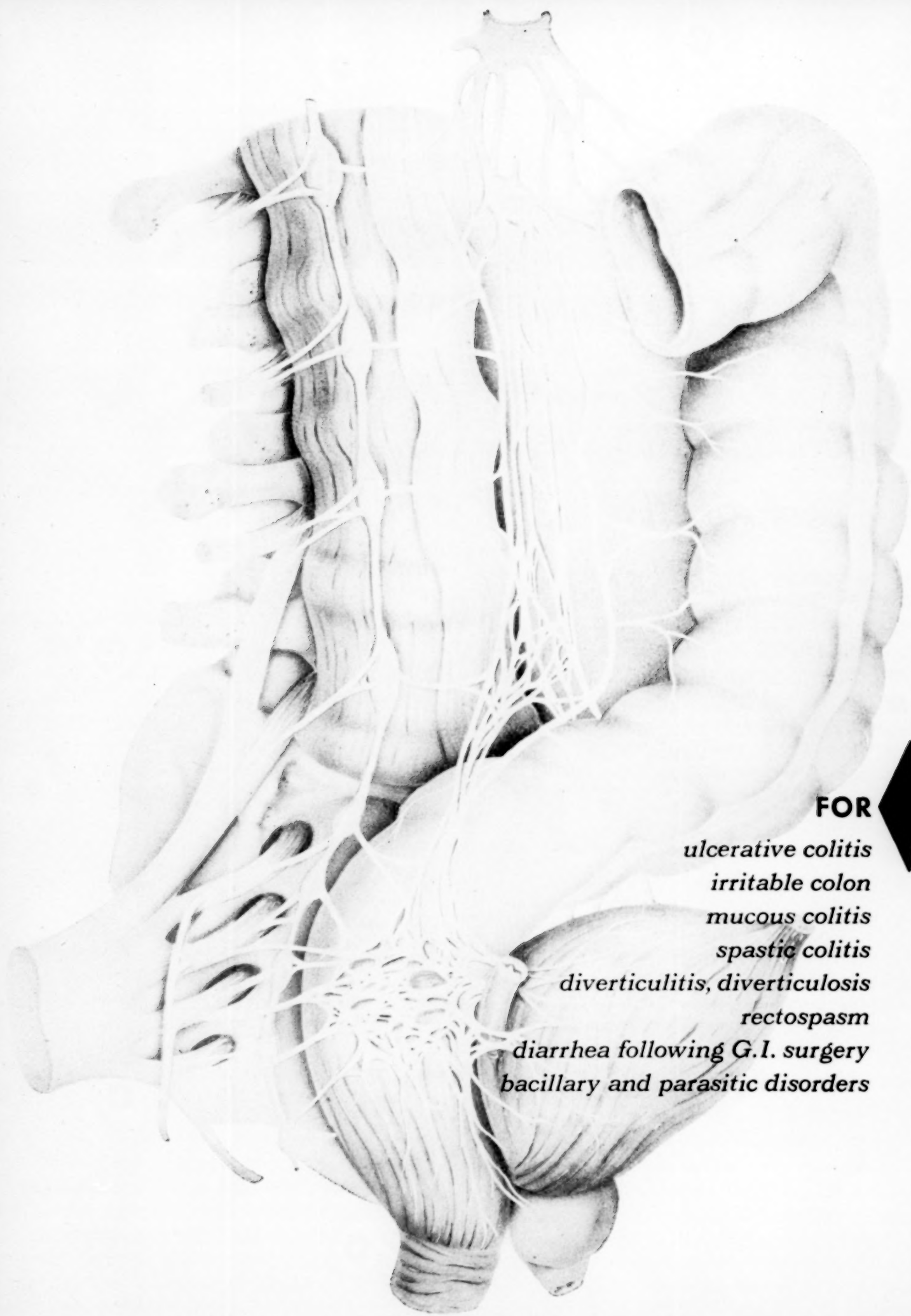
Dexazyme enhances metabolism by providing niacin, thiamine, riboflavin and ascorbic acid.

*brand of pentylenetetrazol



Rx Dexazyme #60 Sig.: 1 (or 2)
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EFFECTIVE

relieves pain, cramps, bloating
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SELECTIVE

avoids widespread autonomic disturbance
unusually free of "antispasmodic" side effects
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CANTIL has a markedly selective anticholinergic action on the colon with little or no effect on stomach, small intestine and bladder. In clinical studies 3 out of 4 patients obtained relief of symptoms and less than 10 per cent had any significant side effects.

HOW CANTIL IS PRESCRIBED

One or two tablets three times a day preferably with meals and one or two tablets at bedtime.

CANTIL—TWO FORMS

CANTIL (plain) — 25 mg. of CANTIL in each scored tablet — bottles of 100.

CANTIL with Phenobarbital — 25 mg. of CANTIL and 16 mg. of phenobarbital (Warning: May be habit forming.) in each scored tablet — bottles of 100.

CANTIL is the only brand of N-methyl-3-piperidyl-diphenylglycolate methobromide.

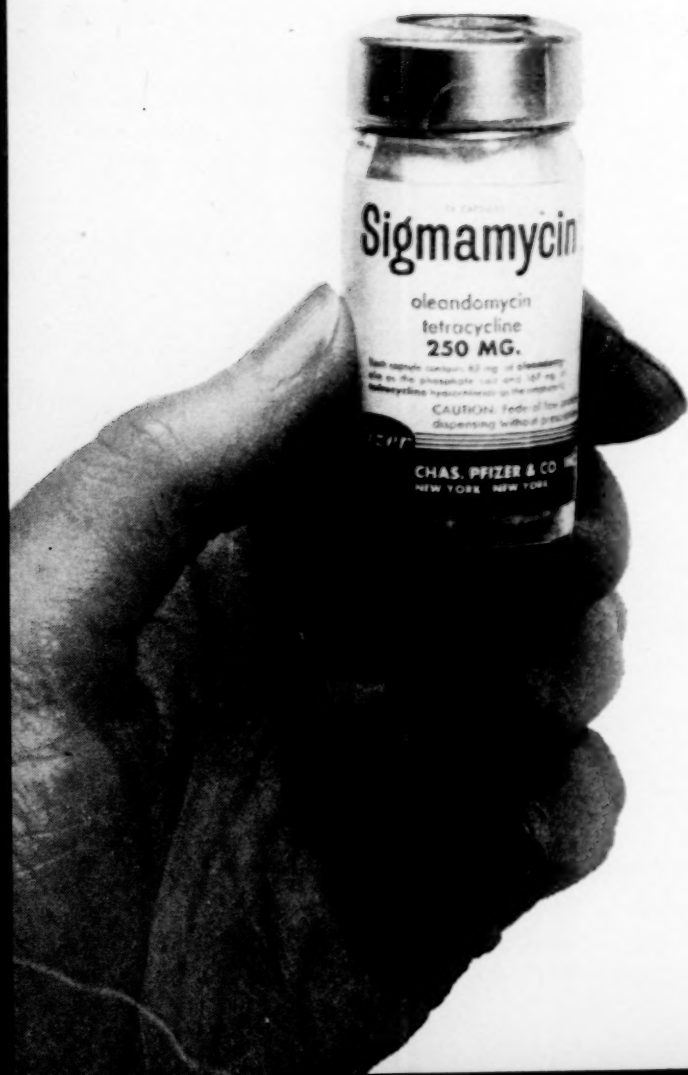
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for added certainty

in antibiotic therapy...

*multi-spectrum[†]
synergistically
strengthened*

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†the antimicrobial spectrum of tetracycline extended and potentiated to include even those strains of staphylococci and other pathogens resistant to previously employed antibiotic therapy; and to provide

1. a new maximum in therapeutic efficacy
2. a new maximum in protection against resistance
3. a new maximum in safety and toleration

Capsules: 250 mg. (oleandomycin 83 mg., tetracycline 167 mg.)



World leader in antibiotic development and production

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plus a new maximum in
palatability... *now available*
with new
mint-flavored
mycin
OLEANDOMYCIN TETRACYCLINE
for ORAL SUSPENSION

A savory mint flavor that adds the further certainty of acceptability to antibiotic therapy, particularly for that 90% of the patient population treated in the home or office where sensitivity testing may not be feasible, and where pleasant flavor can make the difference between prescription adherence and laxity.

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is available in 2 oz. bottles containing 1.5 Gm. of Sigmamycin (oleandomycin 500 mg., tetracycline 1 Gm.). When reconstituted each 5 cc. teaspoonful contains 125 mg. of Sigmamycin (42 mg. of oleandomycin as the phosphate salt with tetracycline amphoteric equivalent to 83 mg. of tetracycline hydrochloride).

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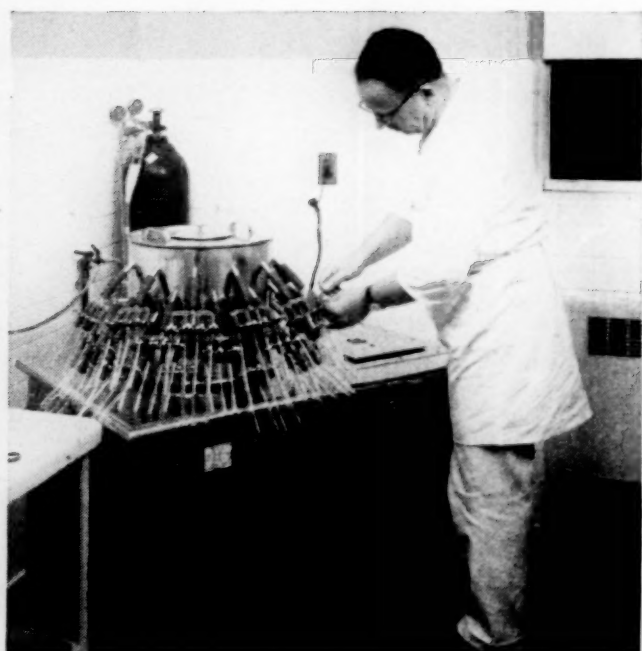
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**preserve precious
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Aminco's renowned Freeze-Dry instruments are being used the world over by research scientists to preserve precious biological specimens and various other types of living cells. The illustration at top left was taken in a U. S. Department of Agriculture Laboratory where an ingenious arrangement was developed to freeze-dry simultaneously 100 samples of *Brucella-abortus* culture, ultimately used for inoculation of cattle.

At bottom left, a University of Maryland scientist uses an Aminco Freeze-Dry to preserve virus, in research work being conducted on the common cold.



Aminco manufactures three models of Freeze-Dry instruments: the **Universal** (Cat. No. 5-7800; \$2,730), which is a complete Freeze-Dry Laboratory incorporating a special freezing compartment for shell-freezing samples and a self-contained refrigeration unit; the **Laboratory Model** (Cat. No. 5-7810; \$1,750), which is built on a smaller scale than the Universal, designed for laboratories with limited floor space; and the small **Bench Model** (Cat. No. 5-7820; \$896), which takes up only 22 x 25 x 28 inches of bench space.

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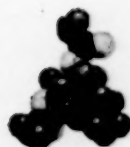
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SUPPLIED: 400 mg. scored tablets. *Usual dose: 1 or 2 tablets i.i.d.*

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for normal, healthy, comfortable pregnancies



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DRY-FILL CAPSULES WITH "BUILT-IN"
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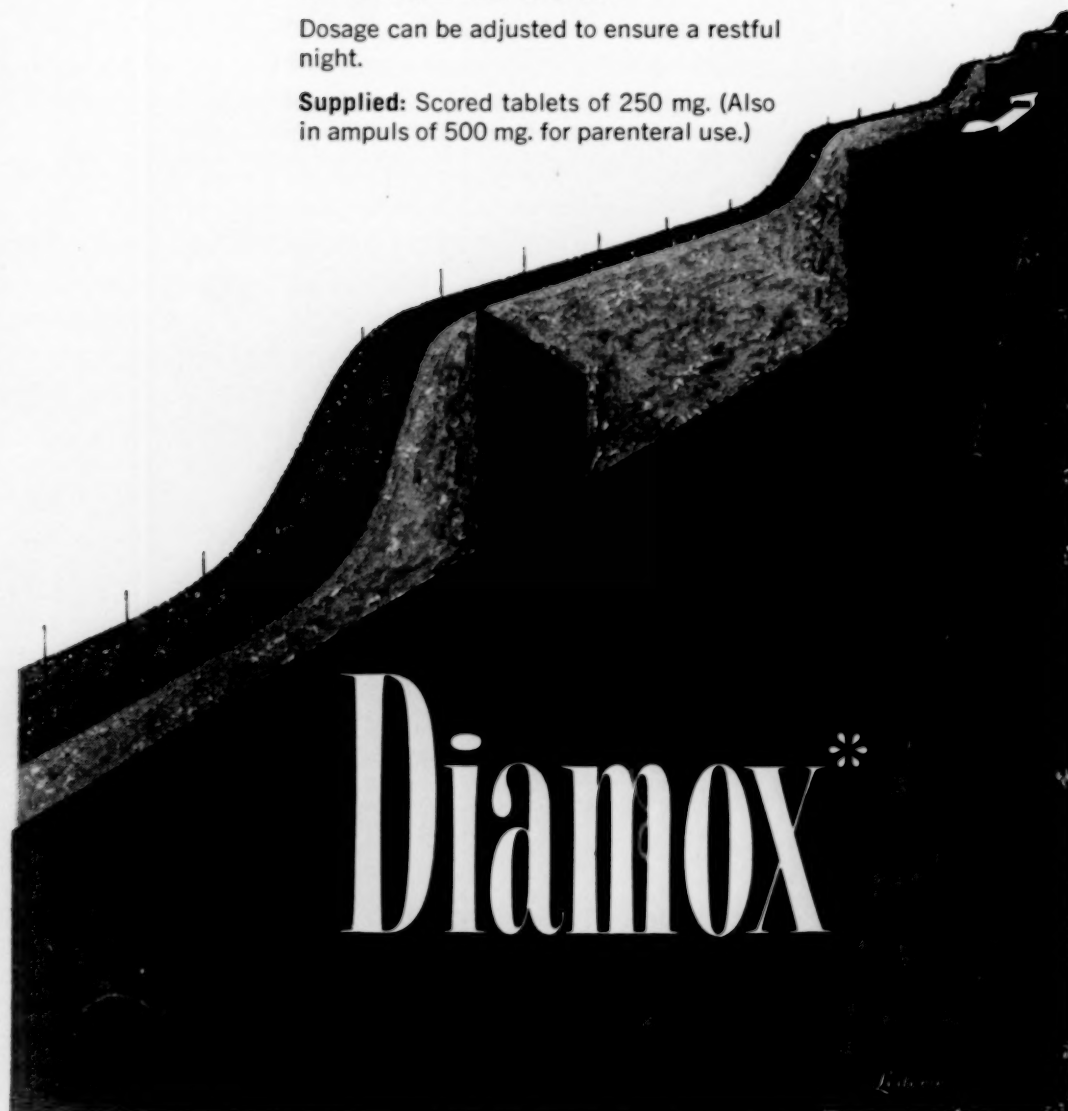
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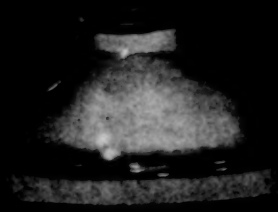
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*Southworth, J. L., and Dabbs, C. H.: Xylocaine: a superior agent for conduction anesthesia, *Anesth. & Analg.* 32:159 (May-June) 1953.

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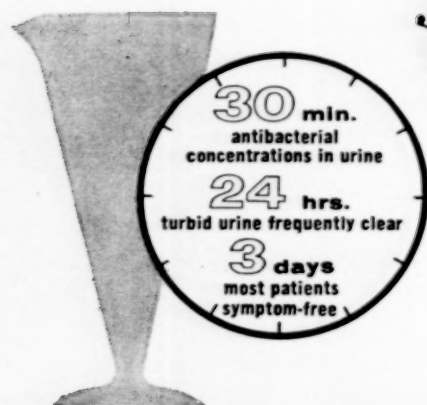
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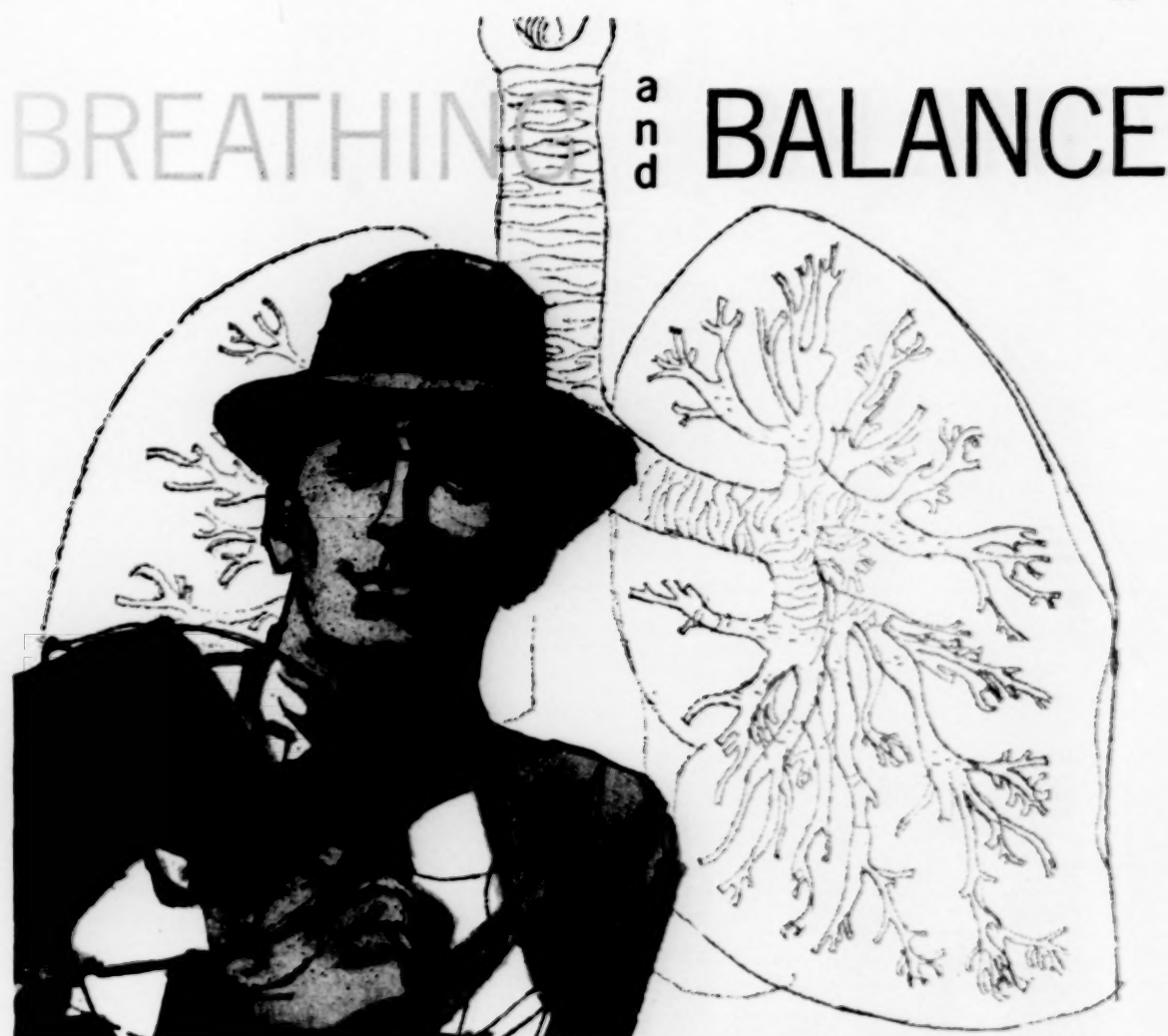
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*Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. **160**:1221, 1956.



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*Schwartz, E.: New York J. Med. 56:570, 1956.

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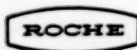
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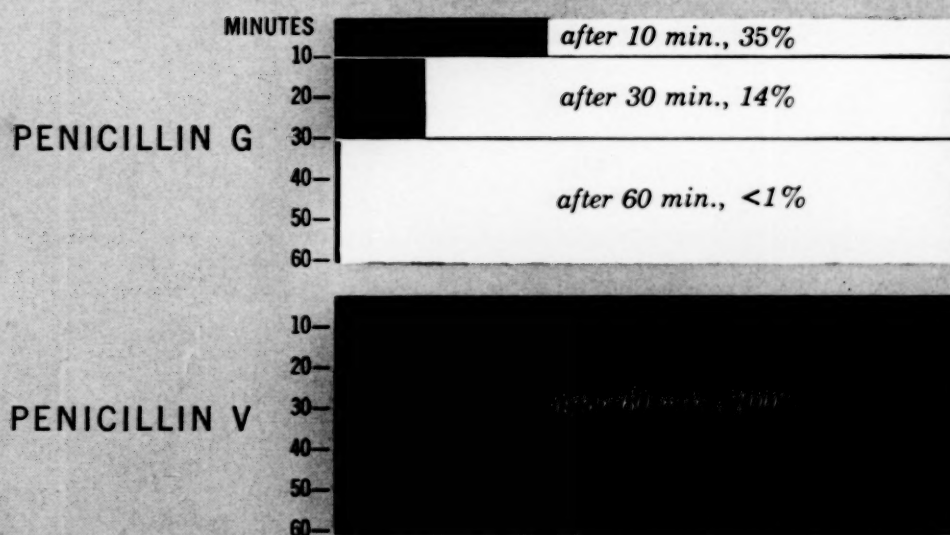
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The American Journal of Medicine

VOL. XXII

JANUARY, 1957

No. 1

Editorial

Cardiovascular Shunts

IN the seventeenth century when Cesalpino¹ and then Harvey² presented the thesis that the blood circulates, it remained for the anatomist to define the channels of circulation. The heart, the large arteries and veins had been studied for centuries but it was necessary to postulate capillaries to explain what were believed to be all the facts at that time. The discovery of the capillaries by Malpighi³ thus seemed to make the entire system clear. It was not until two centuries later that it was realized this rather rigid picture was incomplete.

In the latter half of the nineteenth century Sucquet⁴ and then Hoyer⁵ described tiny communications between small arteries and veins which were shunting mechanisms and, if the thickness of their walls was an index, were not concerned with diffusion between blood and tissues. After another hundred years of effort it now becomes clear that such small arteriovenous communications are normal components of the vascular system of most tissues and add to the flexibility of the circulation in adjusting to changes in the external as well as internal milieu.^{6,7}

This teleologic analysis, however, does not explain the mechanism for the formation and growth of these shunts in fetal life. Their subsequent function also is only partially understood. In the skin of the fingers and toes, for example, these anastomoses are believed to be important in heat regulation, whereas their exact function in the lung or kidney remains unclear. Perhaps they provide safety valves for the protection of capillaries from excessive and possibly damaging blood pressure and perfusion. Although tiny arteriovenous shunts normally occur in most tissues they are more numerous and larger in some parts of the body than in others. In the digits, there are about 450 per square centimeter of skin⁸ and when the blood vessels are fully dilated they may carry more than 90 per cent of the blood flow to the digit. The walls of these glomera are very muscular and are under sympathetic nervous (adrenergic) control. The exact amount of blood perfusing such anastomoses in other tissues is not known.

Shunts between large blood vessels and within the heart, such as the ductus arteriosus and the foramen ovale, are normal only during fetal life. Patent ductus arteriosus and septal defects are in effect persistent and hence abnormal cardiovascular shunts. Auricular and ventricular septal defects usually produce shunts from left to right; but in large defects there may be both left to right and right to left admixture. Right to left admixture occurs in many congenital lesions but most commonly in the tetralogy of Sandifort⁹ (Fallot) in which a septal defect is

BERGMAN, H. C. Arterio-venous anastomoses in liver, spleen and lungs. *Am. J. Physiol.*, 152: 48, 1948.

⁸ GRANT, R. T. and BLAND, E. F. Observations on arteriovenous anastomoses in human skin and in the bird's foot, with special reference to the reaction to cold. *Heart*, 15: 385, 1929-1931.

⁹ SANDIFORT, E. *Observationes Anatomico-Pathologicae*, vol. 1. Leyden, 1777. P. v.d. Eyk and D. Vygh.

¹ CESALPINO, A. *Quest. Medic.*, vol. 2, chap. 17, 1593. Cited by Castiglione, A. *A History of Medicine*. Translated by Krumbhaar, E. B. New York, Knopf, 1941.

² HARVEY, W. *Exercitatio anatomica de motu cordis et sanguinis in animalibus*. Frankfurt, 1628. William Fitzer.

³ MALPIGHI, M. *De pulmonibus. Epistolae II ad Borellium*. Bologna, 1661.

⁴ SUCQUET. Cited by Popoff, N. W. The digital vascular system; with reference to the state of glomus in inflammation, arteriosclerotic gangrene, diabetic gangrene, thrombo-angiitis obliterans and supernumerary digits in man. *Arch. Path.*, 18: 295, 1934.

⁵ HOYER, H. Über unmittelbare Einmündung kleinster Arterien in Gefäßäste venösen Characters. *Arch. f. mikr. Anat.*, 13: 603, 1877.

⁶ CHAMBERS, R. and ZWEIFACH, B. W. Capillary endothelial cement in relation to permeability. *J. Cell. Comp. Physiol.*, 15: 225, 1940.

⁷ PRINZMETAL, M., ORNITZ, E. M., JR., SIMKIN, B. and

associated with overriding aorta and pulmonary stenosis. Surgical correction of a left to right shunt usually consists of repair of the defect. In a right to left shunt a compensating left to right shunt may be established as in the Blalock-Taussig¹⁰ or Potts-Smith-Gibson¹¹ operations, chiefly to provide for increased pulmonary blood flow and hence a higher proportion of oxygenated blood in the systemic circulation. The price for this kind of procedure is an increased circulatory burden on the heart with danger of subsequent congestive heart failure. Increased pulmonary blood flow can also be achieved by direct attack on the pulmonary stenosis¹² but, more recently, adequate extracorporeal circulatory techniques have made it possible to repair both the defect and the stenosis directly.¹³

The major known causes for the development of abnormal shunts between vessels¹⁴ are trauma, infection and tumors. The popliteal, femoral or brachial arteriovenous shunt produced by a bullet or knife is known to most physicians. Familiar also are communications produced between the aorta and superior vena cava or between the aorta and pulmonary artery by syphilitic or other varieties of aortic aneurysm. What is not generally appreciated is that the multiple congenital arteriovenous shunts seen in so-called cirroid aneurysms may also be caused by trauma or infection involving the fetus; also, in adulthood, multiple arteriovenous and other intervascular communications may be caused by chronic infection, especially in such structures as liver, lung, bone and skin. Such shunts, for example, are known to be produced in the lung by bronchiectasis. In bone, Paget's disease may have the same effect. Sometimes, when shunts in a disease such as cirrhosis of the liver have been

present for a sufficiently long period of time, angiosarcomatous growth may take place either uni- or multicentrically. Multicentricity of angiosarcomatous development is also seen in Kaposi's disease of the skin which may be a special manifestation of this kind of process. Metastases from such tumors also occur but are relatively uncommon. The Osler-Weber-Rendu syndrome may be explicable on the basis of a congenital process of a similar character.

In fact, it is fairly safe to say in the light of our recent knowledge^{15,16} that most vascular nevi represent abnormal communications between vessels; not necessarily always artery to vein or arteriole to venule but at times vein to venule, artery to arteriole or any communication between vessels of dimensions improper for the smooth functioning of such a communication. Exact causes for the development of these nevi are not always clear although trauma by pressure or puncture has been implicated. Hormonal factors¹⁷ are believed to be important in the genesis of spider angiomas and the so-called liver palms seen in hepatic cirrhosis and in pregnancy. If the abnormal vessels of a vascular nevus are stimulated for sufficiently long periods of time by abnormal pressure and flow, or possibly by other factors as well, a true new growth may develop. This occurs as neuroangioma or glomus tumor in the skin of the extremities and in other locations as a true angioma or angiosarcoma.

Blood may be shunted through small or larger tumors of the lesser circulation to produce clubbing or hypertrophic osteoarthropathy exactly as in congenital or traumatic arteriovenous fistula of the lung. Many tumors of tissues supplied by the greater circulation, especially hypernephromata or sarcomata, often act as if they are the site of large arteriovenous shunts. Bruits sometimes heard, for example, over such tumors represent turbulent flow, not only through dilated but otherwise normal blood vessels but also through arteriovenous shunts as such.

Abnormal intervascular communications may have profound effects on the circulation as a whole and on the organism. In some cases such a defect may be followed by subacute bacterial

¹⁰ BLALOCK, A. and TAUSSIG, H. B. The surgical treatment of malformation of the heart in which there is pulmonary stenosis or pulmonary atresia. *J. A. M. A.*, 128: 188, 1945.

¹¹ POTTS, W. J., SMITH, S. and GIBSON, S. Anastomosis of aorta to pulmonary artery; certain types in congenital heart disease. *J. A. M. A.*, 132: 627, 1946.

¹² BROCK, R. C. Pulmonary valvulotomy for the relief of congenital pulmonary stenosis. *Brit. M. J.*, 1: 1121, 1948.

¹³ LILLEHEI, C. W., COHEN, M., WARDEN, H. E. and VARCO, R. L. The direct vision intracardiac correction of congenital anomalies by controlled cross circulation. Results in 32 patients with ventricular septal defects, tetralogy of Fallot, and atrio-ventricularis communis defects. *Surgery*, 38: 11, 1955.

¹⁴ HOLMAN, E. Arteriovenous Aneurysm. Abnormal Communications Between the Arterial and Venous Circulations. New York, 1937. Macmillan Co.

¹⁵ MODLIN, J. J. Capillary hemangiomas of the skin. *Surgery*, 38: 169, 1955.

¹⁶ THOMPSON, A. W. and SHAFER, J. C. Congenital vascular anomalies. *J. A. M. A.*, 145: 869, 1951.

¹⁷ BEAN, W. B. The cutaneous arterial spider: a survey. *Medicine*, 24: 243, 1945.

endocarditis or endovasculitis with all the manifestations of this disease. Most of the abnormalities seen, however, are concerned with circulatory function.¹⁴ A communication between an artery and vein, if it is large enough, produces a thrill and murmur which is continuous through systole and diastole with a phasic or machinery-like quality. On the other hand, an interventricular septal defect produces only a systolic murmur and thrill. The nature of the murmur heard over defects in general is affected by the blood pressure relationship between the two communicating vessels both in systole and diastole and in turn by the amount of turbulent flow produced by these pressure differences. The veins draining an arteriovenous communication always become dilated, thickened and tortuous. If the valves become incompetent, this venous change may extend for a variable distance distal to the shunt. The artery also becomes dilated and thickened, and flow through it is increased not only by virtue of the increment through the shunt but also often through the vascular bed as a whole supplied by the involved artery.¹⁵ This may increase the growth of the tissues supplied with blood by this vessel. Systolic and, less often, associated diastolic bruits may also be heard directly over a cirrhotic liver at operation, over a thyroid gland that is hyperfunctioning or over the uterus in normal pregnancy. Here, the placenta acts as if it is the site of large arteriovenous anastomoses. Such sounds represent turbulent flow through the involved vessels and usually indicate that the vessels are dilated and volume flow is increased either through such dilated vessels or directly through a shunt or shunts. This, of course, is responsible for only part of the increase in cardiac output in such diseases as hyperthyroidism or cirrhosis of the liver. Since flow is increased, however, in either the systemic or pulmonary circuit, it becomes correspondingly increased in the opposite circuit because of the operation of the principle of equal output from both ventricles. The work of the heart is therefore increased and if such an increase is sufficiently great or lasts sufficiently long, the heart eventually dilates and fails. The principle of equal ventricular output does not obtain in patent ductus arteriosus where the burden of the increased work caused by increased flow

¹⁴ LEWIS, T. The adjustment of blood flow to the affected limb in arteriovenous fistula. *Clin. Sc.*, 4: 277, 1939-1942.

is on the left ventricle alone. Increase in right ventricular work may, however, be produced by vascular changes in the lung with pulmonary hypertension. The principle of equal ventricular output is also disturbed in septal defects by admixture in both directions and by any factor producing heart failure.

If a systemic arteriovenous communication is sufficiently large, heart rate is increased and pulse pressure, especially proximally, is increased by virtue of increased systolic discharge into the arterial tree as well as increased diastolic leak from it. Closing the fistula decreases cardiac output, slows the heart and raises mean blood pressure. It also decreases systolic and increases diastolic blood pressure. These effects are not only the result of hemodynamic changes incident to closure of the defect but are also influenced by moderator reflexes from the heart, aorta and carotid sinuses.

Closure of an arteriovenous fistula involving the vessels of the lesser circulation is not followed by such reflex effects.¹⁹ If the shunt is large enough, however, the hemodynamic effects of closing the shunt, that is, the decrease in cardiac output and in pulse pressure, are similar to those seen with closure of fistulas between vessels of the greater circulation.

Shunts between vessels of the lesser circuit have special hemodynamic effects. They may, under some conditions, produce clubbing and even hypertrophic osteoarthropathy, a circulatory disease involving vessels of the greater circulation.²⁰ These conditions are believed to occur whenever the left ventricle delivers more blood than is necessary to meet the needs of the tissues supplied by the greater circulation. The excessive blood produces increased pressure and flow and hence tissue growth in the digits and later, if the excess cannot be absorbed by the digits alone, in the periosteum of the bones. Such shunts also produce systemic arterial anoxemia of variable degree, depending on how much of the excessive pulmonary blood flow is going through shunts unoxygenated and how much through the distended but normally aerated pulmonary capillaries. Arterial anoxemia of moderate degree does not produce tissue anoxia in the resting state unless a critical point has

¹⁹ TAKARO, T., ESSEX, H. E. and BURCHELL, H. B. Experimental pulmonary arteriovenous fistula. *Am. J. Physiol.*, 165: 513, 1951.

²⁰ MENDLOWITZ, M. *The Digital Circulation*. New York, 1954. Grune & Stratton.

been passed. The effect of tissue anoxia in producing capillary dilatation and in increasing or retarding tissue metabolism would tend to complicate the mechanism responsible for clubbing, whereas secondary polycythemia would tend to counteract the effect of anoxemia.

Shunts also occur between vessels of different vascular systems. A small amount of blood for example is interchanged between lesser and greater circuits in the lung because of the intermingling of the bronchial and pulmonary circulations. Under abnormal conditions such interchange may become of considerable magnitude. In the liver, the hepatic artery may shunt blood into larger radicals of the portal vein instead of draining into the hepatic vein. Also the portal venous system may be surgically anastomosed with the systemic venous system via shunts created to decompress portal hypertension.

Under certain abnormal conditions blood is also shunted between artery and artery or between vein and vein. Such collateral channels bridge the gap made by closure or constriction of an artery or vein. More direct communication through an artery or vein is provided by recanalization, although the recanalized vessel is always narrower than it was originally. In large veins communication may be reestablished not only by recanalization of the lumen but also by the development of multiple venules on what

appears to be the external surface of the vein. This process is known pathologically as cavernomatous transformation and occurs especially in the portal venous system.²¹ This was at one time considered by pathologists to be a vascular tumor rather than a response to obstruction of a large venous bed. Dissecting aneurysms represent abnormal shunts through the walls of the aorta or a large artery. Direct artificial communications may also be made surgically²² to repair aneurysms of various types and to bridge gaps produced by arterial or venous closures. These have the advantage of preserving the diameter of the original lumen.

It can be seen from these considerations that the subject of cardiovascular shunts is a very broad one extending into many branches of medicine and surgery. It is a rapidly expanding field of interest for students in various disciplines concerned with the understanding and treatment of cardiovascular disease.

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²¹ KLEMPERER, P. Cavernomatous transformation of the portal vein. *Arch. Path.*, 6: 353, 1928.

²² CRAWFORD, E. S., CREECH, O., JR., COOLEY, D. A. and DEBAKEY, M. E. Treatment of arteriosclerotic occlusive disease of the lower extremities by excision and graft replacement or by-pass. *Surgery*, 38: 981, 1955.

Clinical Studies

Multiple Myeloma and the Adult Fanconi Syndrome*

I. Report of a Case with Crystal-like Deposits in the Tumor Cells and in the Epithelial Cells of the Kidney

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THE Fanconi syndrome has been attributed to a defect in the proximal convoluted tubules of the kidney with resulting failure of reabsorption from the glomerular filtrate of substances including glucose, phosphate, amino acids, bicarbonate, and possibly potassium and uric acid. Its cause is unknown. In children it is familial, is associated with cystine storage, and may have a different pathogenesis. In the adult only seventeen cases have been reported,¹⁻¹⁸ in none of these patients was cystine storage demonstrated. The syndrome has been characterized by osteomalacia with multiple fractures and pseudofractures, hypophosphatemia, elevated alkaline phosphatase, massive generalized aminoaciduria with normal plasma amino acid level, renal glycosuria, albuminuria, alkaline urine, mild systemic acidosis, occasional low potassium and low uric acid levels in the serum, and deteriorated renal tubular function in the face of a normal or slightly diminished glomerular filtration. A detailed review of known cases of adult Fanconi syndrome with discussion of the etiologic factors is presented in an accompanying paper.¹⁹ In one of these patients, reported by Sirota and Hamerman,¹⁴ multiple myeloma was also present but was considered a separate disease. In the case which forms the subject of this communication both the adult Fanconi syndrome and multiple myeloma were evident, and the possibility that they were related could not be excluded.

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CASE REPORT

A thirty-eight year old white man (History No. 654371) first entered the New York Hospital in April, 1953, with a three-year history of easy fatigue and nocturia. Nineteen months prior to admission proteinuria was discovered on the occasion of a routine insurance examination. Four months before admission the patient began to bruise easily and was found to be anemic. Three months later numbness and occasional cramps in the legs developed. Ten days before admission the patient fainted, fell, and thereafter noted marked soreness of the ribs. There was a 15 pound weight loss in one year.

The family history was unremarkable except that "diabetes" had developed in several paternal relatives. Past history revealed marked susceptibility to infections and frequent colds. In childhood he had had an abscess of the thorax, pneumonia, "rheumatic fever" and chronic otitis media with mastoiditis and hearing loss. In adult life painful and frequently bleeding hemorrhoids developed.

On examination the patient was pale and thin. He had ecchymoses over the anterior tibial areas. Examination of his ears revealed bilateral conduction deafness and scarred, perforated ear drums. There was point tenderness over the left anterolateral thorax and a slight deformity of the sternum. His blood pressure was within normal limits and no organic defects were detected.

The hemoglobin was 9.8 gm. per cent, red blood cell count 3,500,000 per cu. mm., and the white blood cell count was 8,000 per cu. mm. with 32 per cent lymphocytes, 5 per cent monocytes, 54 per cent mature polymorphonuclear leukocytes and 9 per cent band

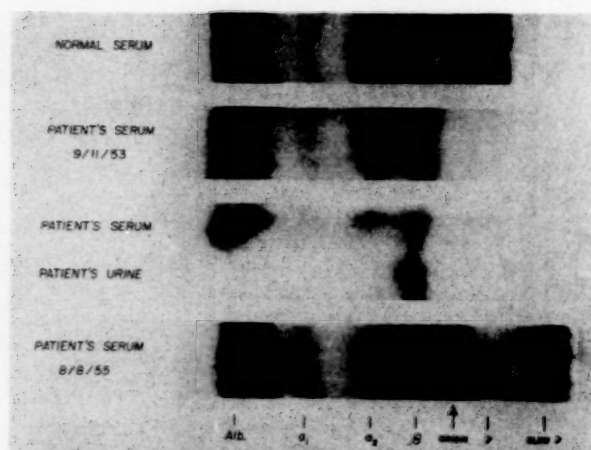


FIG. 1. Filter paper electrophoresis patterns stained for protein with naphthalene black B200. (Veronal buffer, pH 8.5, ionic strength 0.05, room temperature.)

forms. The platelets appeared adequate and normal on smear. There were 2 normoblasts per 100 white cells. The erythrocyte sedimentation rate was 38 mm. in one hour (Wintrobe). The bleeding time, clotting time, clot retraction and tourniquet test were normal; the platelet count was 263,000 per cu. mm. Later studies on several occasions showed no significant change except a moderate decrease in platelets. The blood fibrinogen level was elevated to 568 mg. per cent.

The urine was alkaline, specific gravity 1.028. There were large quantities of protein, moderate amounts of sugar, no acetone. The sediment contained occasional red and white blood cells and many granular casts. The twenty-four-hour urine volume was greater than 3,000 cc. and the specimen was positive for Bence-Jones protein. At pH 5.0 this protein precipitated upon heating to 60°C. and redissolved upon boiling. The patient excreted between 10 and 20 gm. of the urinary protein in twenty-four hours, as measured by the biuret method. The blood urea nitrogen was 9 mg. per cent. Urea clearance was unimpaired. Phenol-sulfonphthalein excretion in two hours was 70 per cent initially and later 45 per cent. The fasting blood sugar was 88 mg. per cent; serum calcium varied between 8.6 and 10.3 mg. per cent; phosphorus was 2.6 mg. per cent; alkaline phosphatase was 6.5 Bodansky units; acid phosphatase 0.4 units. The serum cholesterol was 214 mg. per cent with 75 per cent esterification. The cephalin flocculation test was negative; serum bilirubin 0.76 mg. per cent, 0.21 mg. per cent direct and 0.55 mg. per cent indirect. The serum total protein was 5.4 gm. per cent with 4.1 gm. per cent albumin and 1.3 gm. per cent globulin. There was no cryoglobulin in the serum. The Congo red test was negative.

Filter paper electrophoresis of the serum proteins revealed a marked reduction in the gamma globulin. (Fig. 1.) The urine showed a protein of beta mobility,

a trace of gamma globulin and no appreciable albumin. When a mixture of serum and urine was analyzed by this method, the principal urinary protein component migrated with the beta globulin of the blood.

The electrocardiogram was normal. X-rays of the chest, gastrointestinal tract and skeleton were unremarkable.

Sternal bone marrow obtained by aspiration was hypocellular, with a total count of 7,000 nucleated cells per cu. mm. Megakaryocytes were slightly reduced in number. There were 30 per cent abnormal plasma cells, most of which contained several unusual needle- and rod-shaped cytoplasmic inclusion bodies staining pink with Wright-Giemsa stain. (Fig. 2.) There were also 1 to 2 per cent large reticulum cells which contained many pink-staining rectangular inclusions. (Fig. 3.) When the peripheral smear was closely inspected, 2 to 3 plasma cells containing inclusions could be detected per slide. Although attempts were made to determine the nature of the cytoplasmic bodies, analysis was difficult because of the solubility of inclusions in hot and cold water, normal saline solution, normal serum, the patient's serum, acetic acid, hydrochloric acid, and dilute and concentrated nitric acid. The bodies stained pink with Wright-Giemsa stain, and in supravital preparations they readily picked up the neutral red dye and stained bright red. The nature of the bodies could not be definitely determined. They did not show the property of double refraction and, although they appeared to be crystals, it was impossible to be certain. They were either not stained or were dissolved during the following procedures: peroxidase stain,²⁰ Congo red stain,²¹ toluidine blue stain after formol fixation,²² periodic acid-Schiff reaction after ethanol fixation,²³ Sudan black B stain after fixation in formol-calcium-cobalt,²⁴ Sakaguchi stain for arginine,²⁵ Millon stain for tyrosine,²⁶ sodium cyanide-nitroprusside stain for cystine,²⁷ and the ninhydrin stain. It was concluded that the crystals were not amino acids such as cystine or tyrosine.

By two-dimensional paper chromatography²⁸ the urine showed greatly increased amounts of all amino acids, especially glycine, alanine, glutamine, cysteine acid (cystine), lysine, serine and citrulline. (Fig. 4.) Normal urine in comparable amounts studied by this technic showed only faint traces of alanine, glycine and glutamine. (Fig. 5.) Similar studies on the members of the patient's family (mother, brother and two children) revealed no abnormal aminoaciduria. The crude nitroprusside test for cystine in urine was positive. The alpha-amino nitrogen excreted in the urine amounted to 1,154 mg. per twenty-four hours (normal is between 200 and 600 mg. per twenty-four hours). The plasma amino nitrogen level was low, 2.6 mg. per cent (normal values 4.0 to 7.0 mg. per cent). This pattern of generalized aminoaciduria without aminoacidemia resembled that seen in the

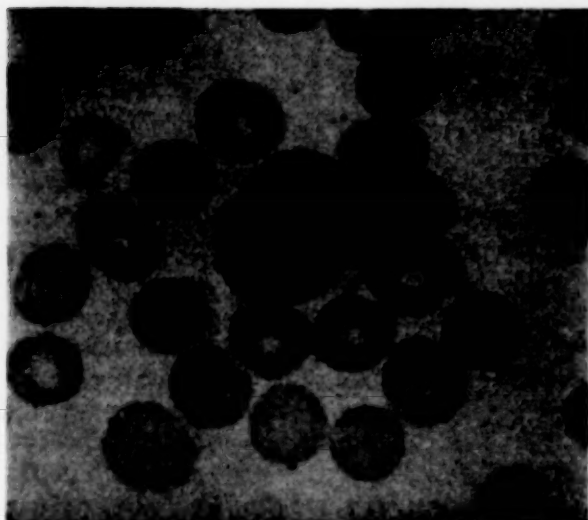


FIG. 2. Bone marrow smear stained with Wright-Giemsa stain showing plasma cell containing rod-shaped cytoplasmic inclusions. Original magnification $\times 1600$.

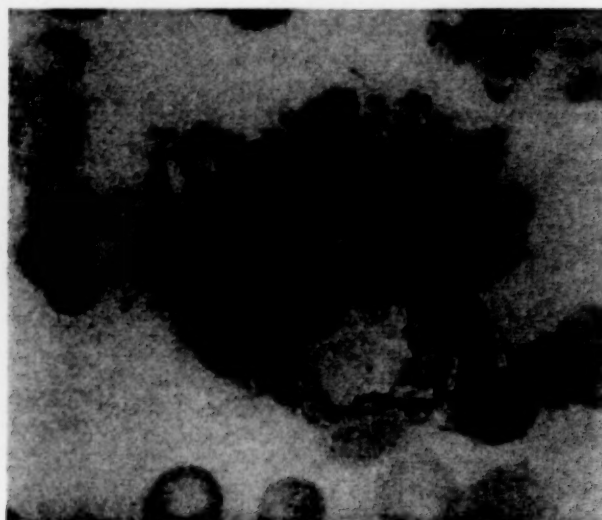


FIG. 3. Bone marrow smear stained with Wright-Giemsa stain showing reticulum cell filled with rectangular cytoplasmic inclusions. Original magnification $\times 1600$.

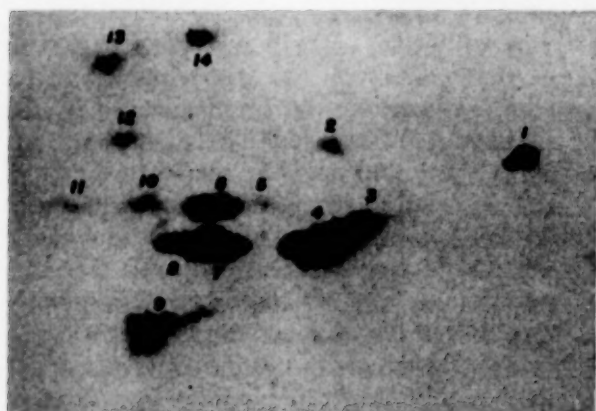


FIG. 4. Two dimensional paper chromatogram of urine stained with ninhydrin for analysis of amino acids. The urine has been placed on a spot at the lower right hand corner of the figure. Phenol was allowed to run from right to left followed by lutidine from bottom to top. The spots were developed with 1 per cent ninhydrin in butanol. Patient's urine: (1) cysteic acid (from cystine), (2) taurine, (3) serine, (4) glycine, (5) threonine, (6) alanine, (7) glutamine, (8) citrulline, (9) lysine, (10) histidine, (11) methyl histidine, (12) valine, (13) phenylalanine and (14) tyrosine.

Fanconi syndrome. Other aspects of that possibility were then further examined.

A reducing substance was constantly found in the urine. Application of the orcinol test for pentose, resorcinol test for fructose, and phenylhydrazine test for crystals of osazone enabled us to rule out the presence of other sugars and to identify the reducing substance positively as glucose. The fasting blood sugar determined several times was normal. The glucose tolerance curve was mildly diabetic (fasting level 84 mg. per cent; one-half hour, 216; one hour,

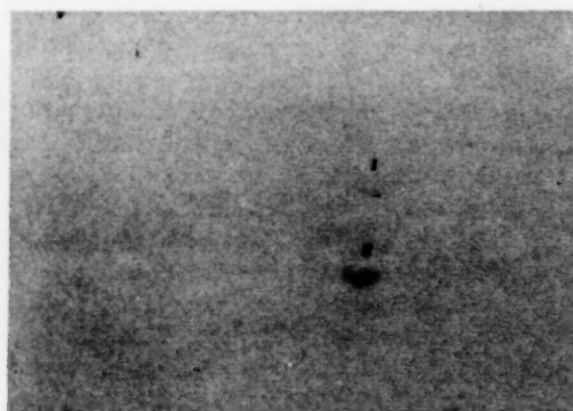


FIG. 5. Two dimensional paper chromatogram of urine stained with ninhydrin for analysis of amino acids. The urine has been placed on a spot at the lower right hand corner of the figure. Phenol was allowed to run from right to left followed by lutidine from bottom to top. The spots were developed with 1 per cent ninhydrin in butanol. Normal urine: (1) taurine, and (2) glycine.

204; two hours, 140; three hours, 56; four hours, 63 mg. per cent). Glucose was present in all urine specimens. During the test an episode of sweating, weakness, substernal pressure and slight drop in blood pressure developed. There was no tachycardia. The serum potassium drawn during that episode was 3.2 mEq./L. and the electrocardiogram showed abnormality of T waves and RT segments and a slightly prolonged QT time suggestive of hypopotassemia.*

* Similar episodes of sudden and sometimes severe peripheral collapse have been observed repeatedly in Fanconi disease.²⁹⁻³² One of them was fatal.²⁹ Earlier authors interpreted collapse as "hypoglycemic shock." It may be better explained as a result of hypopotassemia.

The serum and urinary electrolytes were re-examined. The serum potassium was low normal, 3.7 mEq./L. The serum carbon dioxide content varied between 21 and 17 mM/L. The serum chloride was 104 mEq./L., serum sodium 142 mEq./L., uric acid 1.4 mg. per cent. The serum alkaline phosphatase ranged from 6.5 to 14 Bodansky units. The serum calcium varied between low normal and normal (8.8 to 10.3 mg. per cent). The serum phosphorus varied between 2.0 and 2.6 mg. per cent, while phosphorus excretion in the urine was 428 mg. per twenty-four hours (normal). The urinary calcium excretion in twenty-four hours was low, 39 mg. (normal, 100 to 300 mg.). The urinary excretion of creatinine on the same sample was 1,000 mg., urinary sodium 4,650 mg., urinary potassium 4,950 mg. per twenty-four hours. Examination of the eyes with a slit lamp, performed because of the appearance of cystine crystals in the cornea of patients with the childhood type of the Fanconi syndrome, was negative.

Course. The patient was considered to have multiple myeloma. A small dose of cortisone was administered for two weeks and the ecchymoses disappeared and did not return upon withdrawal of cortisone. In June, 1954, administration of urethane, 2 to 3 gm. a day, was started; it was discontinued after three months because of the development of leukopenia of 2,300 white blood cells per cu. mm. Periodic transfusions were given. In the course of his illness variable pain in the lumbar spine, rib and legs, a waddling gait, increasing exhaustion, frequent nosebleeds, skin pigmentation and hepatosplenomegaly developed. The x-ray films revealed generalized bone demineralization and fractures of several ribs.

After the diagnosis of the adult form of the Fanconi syndrome was made the patient was maintained on a regimen consisting of potassium citrate, 6 gm. a day, premarin,[®] 9 mg. a day and vitamin D, 50,000 units a day. Later, methyltestosterone, 25 to 50 mg. per day was added. Symptomatic improvement resulted which permitted continuance of his work for over a year. He continued, however, to lose weight, and the loss of protein in the urine rose to 50 to 55 gm. per day. Epistaxes and occasional bleeding from hemorrhoids persisted. More frequent blood transfusions were needed to maintain a hemoglobin level of 8 to 10 gm. per cent. In March, 1955, bleeding from hemorrhoids became frequent and massive and failed to respond to a medical regimen. He was therefore admitted to the hospital for ligation or cauterization of the hemorrhoids.

At this time the patient was found to be jaundiced and a few spider angiomas were seen on the trunk. The serum total bilirubin was 6.8 mg. per cent with 1.6 mg. per cent direct and 5.2 mg. per cent indirect. Thymol turbidity and cephalin flocculation tests were normal. There was no bile in the urine. Cholesterol esters were only 28 per cent of the total cholesterol. Alkaline phosphatase was 9.4 Bodansky units. The serum protein was 6.0 gm. per cent with 3.7 gm. per cent albumin and 2.3 gm. per cent globulin. The Coombs' test was negative. The prothrombin time was normal and the platelet count was 140,000 per cu. mm. X-ray films of the bones now revealed increased rarefaction, punched-out lesions in the ribs, and multiple fractures and pseudofractures of the ribs.

A hemorrhoidectomy was performed. A few days later the patient began to pass tarry stools and then bright red blood by rectum. X-rays of the esophagus, stomach and intestines revealed only hypermotility of the bowel. On proctoscopy a bleeding point was found a few centimeters above the internal hemorrhoidal ring. Ligation of the vessel failed to bring permanent relief, and a transverse colostomy was performed. However the bleeding from the rectum continued intermittently until it was finally stopped by cauterization. During the two-month hospitalization period the patient received approximately fifty units of blood for replacement of blood loss. After discharge diarrhea developed which could be controlled only by large doses of opiates. Meticorten, 10 to 30 mg. per day, was added to the regimen.

The patient's final admission to the hospital in August, 1955, was precipitated by a fracture of the neck of the left femur sustained when he stood up. Four days after admission lethargy, a high fever to 40°C., and shaking chills developed. Numerous colonies of *Escherichia coli* were grown from the blood culture. The organism showed *in vitro* sensitivity to all broad-spectrum antibiotics. However, the patient was given intravenous terramycin[®] and intramuscular streptomycin. Temperature spikes to 39°C. continued. He was digitalized and his fluid and electrolyte balance was controlled. The serum bilirubin rose to 21.1 mg. per cent and the thymol turbidity to 26 units. Acidosis and anuria developed, but the blood urea nitrogen remained low at 9 mg. per cent to within nine days of death. One week before death a slow gamma peak appeared in the paper electrophoretic pat-

tern of the serum. (Fig. 1.) Electrophoresis of the urine continued to show a beta globulin. The patient died on the fourteenth day of his last admission to the hospital.

Autopsy. The skin and scleras were deeply jaundiced and there were multiple purpuric areas over the body. Scattered throughout the parenchyma of the right lung and in the left lower lobe were multiple small nodules, 0.5 to 1 cm. in diameter, which were hemorrhagic, firm and granular. The intervening pulmonary parenchyma was edematous. The spleen weighed 750 gm. and its capsule was smooth and tense. On cut surface the parenchyma was of normal consistency and normal trabecular markings were present. Malpighian corpuscles were not apparent but there were scattered spherical nodules of tan homogeneous tissue in the parenchyma. Some of these measured up to 0.5 cm. in diameter. The liver weighed 2,150 gm. and had a normal consistency. The capsular surfaces were smooth and glistening. On cut surface the lobular pattern was accentuated by delicate green anastomosing strands, which here and there divided the parenchyma into a slightly nodular pattern. In addition there were nodules of tan tissue, which were even more distinctly demarcated from the surrounding liver and measured up to 1.5 cm. in diameter. The kidneys weighed 440 gm. and were equal in size. The capsular surfaces were smooth and stripped easily. The renal parenchyma was soft and jaundiced, and the cortex quite pale, but the normal architectural markings on the cut surface were clear and distinct. Calyces, pelves and renal vessels were normal. The lymph nodes were everywhere of normal size, although many of them were brown on the cut surface. The marrow of ribs, sternum, vertebrae, iliac crests and left femur contained innumerable sharply demarcated osteolytic lesions, which measured from 0.2 to 1.5 cm. in diameter. In many places there was erosion of cortical bone and multiple healed fractures of the ribs. Vertebral bodies were intact. Osteolytic areas contained pale yellow, soft, gelatinous tissue. The surrounding marrow was light red and more normal in appearance. Skull was normal to transillumination. Remaining organs were grossly normal.

Microscopic examination of the lung revealed focal areas of necrosis which were infiltrated by neutrophils and bacteria. Much fibrin was seen in some of the alveolar spaces. The remaining alveoli contained many dust cells, a few

were filled with a pale pink granular coagulum. The white pulp of the spleen was well maintained but the red pulp was quite hyperemic and contained a diffuse infiltration of plasma cells. In the sinusoids were focal groups of phagocytes containing much hemosiderin. A few plasma cells and reticulum cells contained rod-shaped cytoplasmic inclusion bodies. In the liver, although the lobular architecture was recognizable, there was marked fibrosis and diffuse scarring involving primarily the central areas. These areas contained a few plasma cells and many other round cells and much hemosiderin. A number of neutrophils were also present and there were a few necrotic liver cells at the periphery of the lobule. A few plasma cells and reticulum cells contained rod-shaped, cytoplasmic inclusion bodies. The adrenals were normal except for the presence of rod-shaped inclusion bodies in some parenchymal cells.

The renal architecture was not markedly altered, although slight interstitial fibrosis, edema, and a few small areas of sclerotic glomeruli and round cell infiltration could be noted. The glomeruli were otherwise normal as were the arteries and arterioles. The tubules, however, were extensively and markedly altered throughout most of their length. They were in most instances quite dilated. A few of them contained large, deeply eosinophilic casts, some of which were laminated. A very rare giant cell was seen at the periphery of these tubules. Many tubules were lined by cells with markedly vacuolated and pale cytoplasm; others were filled by parallel groups of delicate, poorly staining, needle-like cytoplasmic inclusions. (Fig. 6.) With Mallory's connective tissue stain they were pale yellow-green. They stained deep purple with phosphotungstic acid-hematoxylin. The epithelial cells containing these inclusions were most numerous in the cortex near the capsule of the kidney. It was impossible to localize these cells to either the proximal or distal segment because of the marked involvement of whole tubules. The tubular cells, particularly in the loops of Henle, frequently had bizarre nuclei, many of them large, pleomorphic and hyperchromatic. A few cells had two or three nuclei. Many cells were small and flattened while others were large and hypertrophied. The collecting tubules were essentially normal.

The architecture of the lymph nodes was but slightly altered. The sinusoids contained much hemosiderin and many plasma cells. A few

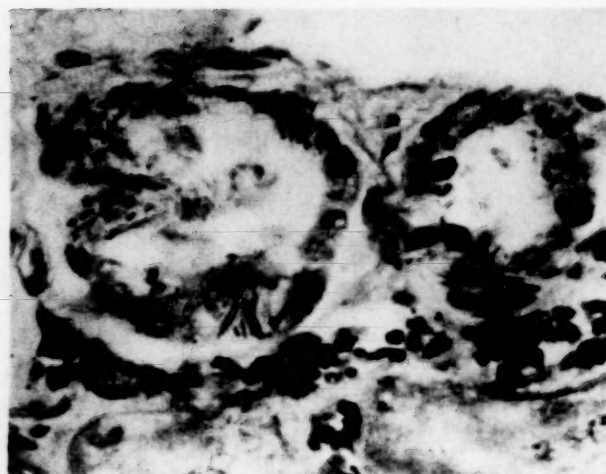


FIG. 6. Section of kidney showing tubular epithelial cells filled with rod-shaped cytoplasmic inclusions; phosphotungstic acid-hematoxylin stain, $\times 650$.

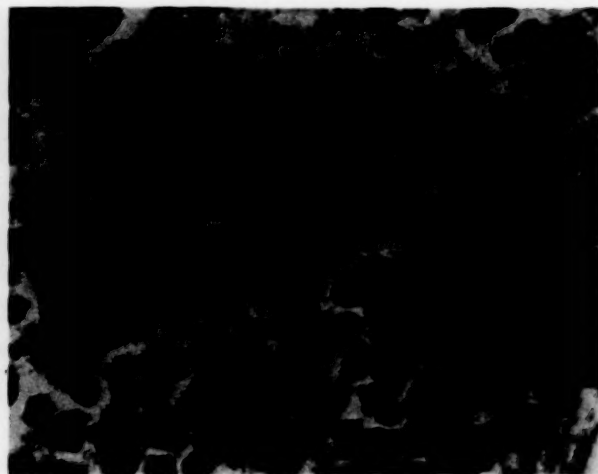


FIG. 7. Section of bone marrow from femur showing plasma cell infiltration and occasional reticulum cell containing rod-shaped cytoplasmic inclusions; hematoxylin and eosin stain, original magnification $\times 650$.

of the plasma cells and an occasional reticulum cell contained rod-shaped, cytoplasmic inclusion bodies. Most sites in the bone marrow were very hypocellular, and in these areas about 90 per cent of the cells were myeloma cells. (Fig. 7.) The myeloma cells had a small amount of basophilic cytoplasm, a peripherally placed nucleus and clumped, coarse chromatin. In addition there were numbers of large pale cells that were probably histiocytes or reticuloendothelial cells. Many of these and occasionally a plasma cell contained rod-shaped cytoplasmic inclusion bodies similar to those already described. In some areas the marrow was markedly hyperplastic, containing large numbers of erythropoietic cells, granulocytes and megakaryocytes. There were well healed fractures of the ribs. Bone resorption was marked throughout.

Touch preparations of the bone marrow, liver, spleen and kidney were made by lightly touching the cut surface of these organs to slides and then staining with Wright or Wright-Giemsa stain. Most of the plasma cells in the bone marrow and spleen as well as the few plasma cells in the liver and some parenchymal cells of the kidney contained the rod-shaped cytoplasmic inclusion bodies. Reticulum cells containing similar bodies were also seen in the bone marrow, liver and spleen.

Autopsy diagnoses were multiple myeloma, myelomatous renal disease, cirrhosis of the liver, passive hyperemia of the spleen, bronchopneumonia, hemosiderosis, multiple hemorrhages and transverse colostomy.

COMMENTS

The clinical picture was a composite of multiple myeloma and adult Fanconi syndrome. Multiple myeloma was manifested by massive plasmacytosis of the bone marrow, Bence-Jones proteinuria, anemia, bleeding tendency, hepatosplenomegaly and osteolytic lesions of the ribs. The diagnosis of adult Fanconi syndrome was established by generalized massive aminoaciduria, low plasma amino acid level, renal glycosuria, mild renal acidosis, hypokalemia, hypophosphatemia, elevated alkaline phosphatase, osteomalacia, multiple fractures and pseudofractures, hypouricemia and normal urea clearance in the face of a decreased phenolsulfonphthalein excretion.

One of the most striking features of this case was the demonstration of crystal-like cytoplasmic inclusions in the plasma cells and reticulum cells of the bone marrow and other tissues. These inclusions differ from others described in plasma cells as colorless greyish blue vacuoles (Mott cells), large eosinophilic globules (Russell⁷bodies^{33,34}) or tiny spindle-like bodies.^{35,36} Only nine cases of multiple myeloma and "reticuloendotheliosis" with comparable intracellular structures in the plasma cells have been found in the literature.^{35,37-41}

In addition rod-shaped cytoplasmic inclusions resembling those seen in the plasma cells were found in the tubular epithelial cells of the kidney. Similar intracellular deposits have been described in several other cases of multiple

myeloma.^{35,46-48} Other types of deposits in the cells of the renal tubules, as well as material in the interstices and within the lumen of the tubule, have often been recorded.⁴⁶⁻⁴⁹ Casts of "Bence-Jones protein" have been seen frequently within the lumen of the distal tubule of the "myeloma kidney."

Three possible explanations for the simultaneous appearance of multiple myeloma and the adult Fanconi syndrome might be considered. As suggested by Sirota and Hamerman¹⁴ myeloma and the adult Fanconi syndrome might be unrelated. However discovery of a second patient in whom the rare entities coexist makes a chance occurrence less likely. A second hypothesis is that our patient had only the adult Fanconi syndrome and that the manifestations of what seemed to be multiple myeloma in reality were previously unrecognized components of the syndrome. It became important, therefore, to determine the incidence of plasmacytosis, serum protein abnormality and Bence-Jones proteinuria in recorded cases of Fanconi syndrome. A review of the literature lent little support to this hypothesis. Fanconi described two childhood cases with peripheral blood plasmacytosis,³⁰ but in three adult patients in whom examinations of bone marrow had been performed there was no plasmacytosis.¹⁹ Among the reported patients with adult Fanconi syndrome there was no serum protein abnormality comparable to that seen in multiple myeloma. Bence-Jones proteinuria was seen only in the patient recently reported by Sirota and Hamerman.¹⁴

Finally, the possibility that the Fanconi syndrome might be secondary to multiple myeloma should be entertained. A number of agents¹⁹ can cause abnormalities similar to those found in the Fanconi syndrome, presumably through their effect on the kidney tubules. The possibility cannot be excluded that the crystal-like inclusions within the tubular epithelium of the kidney or the Bence-Jones proteinuria with its deposits in the tubules and surrounding cells might have caused injury sufficient to create defects in tubular reabsorption.

In an effort to find other patients with multiple myeloma who had the Fanconi syndrome, we have examined urines of thirty individuals with multiple myeloma for aminoaciduria by means of paper chromatography. Eleven of these were excreting appreciable amounts of Bence-Jones protein in the urine at the time. In none, how-

ever, were we able to demonstrate appreciable aminoaciduria.

The coexistence of multiple myeloma and the adult Fanconi syndrome in two patients is sufficient indication to search for signs of the other when one is present. In patients with multiple myeloma the following clues should make one suspicious of the adult Fanconi syndrome: renal glycosuria, low serum phosphorus and elevated alkaline phosphatase. Early detection of an associated adult Fanconi syndrome may permit effective treatment of this complication.

SUMMARY

Report is made of a patient who exhibited signs of both multiple myeloma and the adult form of the Fanconi syndrome. It is suggested that renal tubular reabsorption defects like those of the adult Fanconi syndrome may occur in patients with multiple myeloma. Patients with multiple myeloma, particularly if associated with Bence-Jones proteinuria, deserve close scrutiny for evidences of defective tubular reabsorption.

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The Adult Fanconi Syndrome*

II. Review of Eighteen Cases

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OBSERVATION of an adult with the Fanconi syndrome and multiple myeloma¹ led us to review the recorded cases of the adult Fanconi syndrome and to reconsider its pathogenesis.

The disease in children was initially described by Lignac in 1924,² then by de Toni in 1933,³ by Debré in 1934⁴ and by Fanconi in 1931 and 1936.^{5,6} It has since been found in about seventy children. It is familial, occasionally associated with consanguinity and is probably inherited as a simple Mendelian recessive, with a gene frequency of 1 in 200 and disease incidence of 1:40,000 children.⁷ The syndrome consists of dwarfism, rickets, albuminuria, aminoaciduria, renal glycosuria, hypophosphatemia with hyperphosphaturia, acidosis and late cystine storage. It carries a poor prognosis, death occurring usually before puberty.⁷ This disease is thought by some^{6,8,9} to be due to a congenital enzymatic defect in the proximal convoluted tubules of the kidney with resulting failure of reabsorption of glucose, phosphate, amino acids, bicarbonate, uric acid and potassium. A different point of view is taken by Bickel et al.⁷ who believe that the Fanconi syndrome in children is due to an inborn error in the metabolism of amino acids with resulting storage of cystine and overflow of this and other amino acids in the urine.

Milkman^{10,11} was the first to describe osteomalacia with multiple symmetric fractures, renal glycosuria and hypophosphatemia in an adult. Milkman's syndrome refers to the roentgenologic picture of bony rarefaction and symmetric "pseudofractures." It may occur in osteomalacia of any cause,¹²⁻¹⁴ including the adult Fanconi syndrome. Not all cases reported as roentgenologic Milkman's syndrome fall into the group of the adult Fanconi syndrome, even

though the original case of Milkman did. On the other hand, all patients with the adult Fanconi syndrome do exhibit osteomalacia and the x-ray picture as described by Milkman. Including his report eighteen cases of the adult Fanconi syndrome have been recorded. Criteria for including reported cases in this series have been: osteomalacia with hypophosphatemia and pseudofractures, renal glycosuria and aminoaciduria (when determined) without hyperaminoacidemia occurring in an adult patient.

CASE REPORTS

CASE I. (Milkman.^{10,11}) This forty-one year old woman, a school teacher, was seen in 1928 with increasing lameness and pain in the back and hips on stooping, associated with difficulty on arising for three years. A waddling, painful gait and "diabetes" developed; the patient became bedridden and died at the age of forty-five despite cod liver oil, viosterol and ultraviolet radiation. X-ray films revealed multiple symmetric pseudofractures of the ribs, femurs, pelvis, ulnas and fibulas, and finally also complete fractures. At postmortem examination osteomalacia and increased vascularity at the transparency zone were noted.

CASE II. (Fletcher,¹⁵ reported more fully by Hunter¹⁶ Case 7.) A thirty-four year old bus-conductor was first seen in 1934 with a three-year history of increasing pain in the hips and thighs on walking. The patient had a shuffling gait and constant glycosuria. X-ray examination revealed considerable "osteoporosis" and multiple fractures of the pubic rami, right femur, transverse processes of lumbar vertebrae and the metacarpals. The skull was "woolly" in appearance and had "scattered small patchy areas of osteoporosis in the outer table." Exploration of the neck in 1935, revealed no parathyroid tumor and the biopsy specimen of the left inferior parathyroid gland was interpreted as normal.

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Biopsy of the tibia revealed osteoporosis. The patient showed no improvement on a high calcium diet with large doses of vitamin D.

CASE III. (Hunter,¹⁶ Case 6.) A twenty-nine year old physician was hospitalized in 1931 with a four-year history of progressive pain in the hips, weakness in the legs and difficulty in walking. He gave a past history of rickets in childhood and manifested gross deformities with marked scoliosis. The patient had renal glycosuria and albuminuria. X-ray films revealed "much thinning of bones and gross deformity with old fractures of both pubic bones." In 1933 despite a high calcium diet, calcium lactate and vitamin D, the patient grew weaker and x-ray examination showed "great loss of calcium" with old and recent fractures in the rami of the ischium, femur, ulna, tibia and fibula. Exploration of the neck revealed no parathyroid tumor and the biopsy specimen of the right parathyroid gland was normal. The diagnosis on biopsy of the tibia was osteoporosis and osteomalacia.

CASE IV. (Edeiken.¹⁷) A thirty-four year old American housewife was seen in 1942 with the complaint that for four years she had experienced weakness, cramp-like pains in the left thigh and inability to walk and to arise from a supine, sitting or kneeling position. The patient was dwarfed and had a transient renal glycosuria. The x-ray examination showed "generalized calcium deficiency, punched-out cortical notches and transverse zones of rarefaction traversing part or all of the bone usually at right angles to the long axis." These pseudofractures were seen in the scapulas, clavicles, radius, ulnas, ribs, femurs, tibias and metatarsals.

CASE V. (Cooke.⁸) A thirty-six year old unemployed man was seen first in 1942 because of progressive back pain, stiffness and weakness of the legs and very painful walking for ten years. He was semi-bedridden and x-ray films showed extensive osteoporosis with fractures of the ribs. Laboratory tests revealed persistent glycosuria in the presence of a normal glucose tolerance test, hypophosphatemia and hyperphosphaturia. The patient remained unchanged until 1945 when he died following a hematemeses. Postmortem examination revealed, in addition to a bleeding duodenal ulcer which was the cause of death, thinning of the cortex of the bones. The epithelial cells of the proximal convoluted tubules were vacuolated, some were necrotic, and Gomori's stain revealed absence of alkaline phosphatase in these cells.

CASE VI. (Stowers.⁹) A thirty-four year old surveyor was first seen in 1944 complaining of back pain radiating into both thighs for four years and of increasing difficulty in walking that resulted in a peculiar waddling gait. In 1942 the patient was diagnosed as having diabetes mellitus; however he exhibited faintness and

blurred vision on as little as 10 units of insulin. He was found to have hepatomegaly, albuminuria, aminoaciduria, hypophosphatemia and mild diabetes mellitus with additional renal glycosuria. X-ray films showed "generalized osteomalacia and multiple pseudofractures of the ribs with no callus formation." The patient responded initially to treatment with calcium and high doses of calciferol, with healing of the pseudofractures, decrease in osteomalacia and symptomatic improvement. He discontinued treatment at home and in 1946 died of hematemeses and melena. Postmortem examination revealed primary carcinoma of the liver, patches of osteomalacia of the skull and ribs with excessive bowing in the latter. The epithelium of the proximal convoluted tubules was swollen and vacuolated and did not contain alkaline phosphatase when stained by Gomori's method.

CASE VII. (Linder.¹⁸) A thirteen year old Negro girl seen in 1942 complained of polyuria of 2 to 4 L. for five years. She had gross body deformities, constant renal glycosuria, aminoaciduria and occasional albuminuria. X-ray films revealed generalized osteoporosis and "greenstick fractures." The patient did not improve on citric acid but seemed benefited by high doses of calciferol.

CASE VIII. (Dent.¹⁹) A forty-one year old woman was bothered by pains in her back, hips, ribs and feet for seven years. She had progressive difficulty in walking and became bedridden. This patient had persistent renal glycosuria and aminoaciduria and x-ray films showed multiple "pseudofractures" of the ribs and long bones and some generalized decalcification of the skeleton. On a regimen of alkali, calcium and massive doses of vitamin D, the patient's bone pain diminished and she was able to work. X-ray examination showed healing of pseudofractures.

CASE IX. (Lambert.²⁰) A fifty-six year old man sought hospitalization in 1950 for severe lumbar back pain of eight years' duration with spastic paralysis of his lower limbs for six years. He was unable to move in bed. X-ray examination showed extreme bony decalcification with collapsed vertebrae and with fractures and pseudofractures of his pelvis and femurs. He had renal glycosuria, aminoaciduria and hypophosphatemia. After massive doses of calcium phosphate the patient seemed much improved, was able to move about and sit in bed without help or discomfort. X-ray films showed improvement in mineralization of his bones.

CASE X. (Anderson.²¹) A forty-four year old single woman, a rachitic dwarf, was first seen in 1949 because of pain in her right hip and knee following an injury eight years previously. This pain progressed and the patient was confined to bed and a wheelchair. The x-ray examination revealed marked rarefaction with multiple pseudofractures of femurs, pubic rami, ribs and spinous processes; the x-ray film of the skull

showed "irregularly dispersed patchy thinning." She had aminoaciduria and transient renal glycosuria. On a Shohl's alkalinizing regimen of citric acid-sodium citrate solution and a short course of methyl testosterone the patient improved considerably; she could walk the length of the ward and there was an increase in the density of the bones with nearly complete bridging of all symmetric fracture lines by well developed, new bone.

CASE XI. (Milne.²²) A fifty-one year old widow was seen in 1950 with severe aching pain in the back and in the upper thighs for three years. Her disability progressed to the state of complete immobility in bed. The patient was found to have albuminuria, renal glycosuria, ketonuria, aminoaciduria, acidosis and hypophosphatemia, with hypokalemia suggested by electrocardiography and confirmed on chemical analysis. Radiologic examination of the skeleton showed a generalized reduction in bone density with pseudofractures of the ribs. On a regimen of citrate solution and massive doses of vitamin D and calcium lactate the patient improved markedly, and in five weeks she was able to walk without pain. Bony tenderness disappeared and the pseudofractures recalcified. There was a change in her electrolytes toward normal values.

CASE XII. (Dragstedt.²³) A forty-six year old businessman was first seen in 1952 with a history of easy fatigue and proteinuria for eight years, bone pains and limping gait of one year's duration. His past history included vigorous antisyphilitic treatment with bismuth and salvarsan® twenty-five years before. He was found to have multiple rib fractures, hypophosphatemia, renal glycosuria and aminoaciduria. On an alkalinizing regimen and vitamin D the patient improved markedly and could walk without discomfort. X-ray films showed callus formation at the fracture sites.

CASE XIII. (Sirota.²⁴) A fifty-year old grocer was admitted in 1947 complaining of progressive severe pains in the back, shoulders, ribs and thighs and marked weakness with inability to walk unassisted since 1944. He had proteinuria, renal glycosuria with a normal glucose tolerance test, hypophosphatemia and hyperaminoaciduria with a normal plasma amino nitrogen concentration. The patient did not improve on high calcium, high phosphorus and vitamin D therapy, and when seen in 1951 he had a waddling gait and could hardly manage a few steps. His x-ray films at that time revealed mild generalized decalcification of the skeleton with symmetrical pseudofractures of the scapulas, femoral bones and ribs, without osteolytic lesions. He also was found to have at that time, in addition to deteriorated renal function and hyperchloremic acidosis, a diabetic glucose tolerance curve, Bence-Jones proteinuria, 8 to 10 per cent myeloma cells in the bone marrow, and an ab-

normal peak on serum electrophoresis which migrated somewhat slower than gamma globulin. On a regimen of high calcium diet, vitamin D, calcium lactate, potassium bicarbonate and Shohl's mixture for two months there was some equivocal improvement. After six months of full exposure to Florida sun and massive intake of orange juice there seemed to be a marked subjective improvement with ability to walk freely, healing of pseudofractures and increased calcium deposition.

CASE XIV. (Brick,²⁵ also studied by Kyle.²⁶) In an Army serviceman hip pain developed following a fall at the age of thirty-three. Three years later he was hospitalized for pain in the back and the leg with progressive limping and a waddling gait. Generalized "osteoporosis" and numerous pseudofractures were noted on x-ray examination, involving the vertebrae, ribs, scapulas, radial heads, acetabulums, femurs and both patellas. Intermittent glycosuria and a normal glucose tolerance were found. The patient was considered to have Milkman syndrome of unknown etiology and was treated with vitamins D and A, calcium orally and parenterally, multivitamins and physiotherapy without satisfactory results. When studied last at the age of forty-two, the patient was also found to have aminoaciduria, polyuria, hypophosphatemia and hyperphosphaturia.

CASE XV. (Salassa.²⁷) A sixteen year old boy was hospitalized because of a nine-year history of progressive weakness, fatigue and soreness of legs, necessitating the use of crutches. He was found to have deformities of legs, roentgenologic evidence of demineralization of bones, rachitic changes at the ends of long bones and fractures of the left femur. In addition, he manifested renal glycosuria, albuminuria, aminoaciduria and systemic acidosis. On 400,000 units of vitamin D₂ a day, his pain and weakness slowly decreased, aminoaciduria decreased and the patient was able to walk comfortably without support.

CASE XVI. (Salassa.²⁷) An eleven year old girl was hospitalized because of progressive difficulty in walking, marked deformities, dwarfism and weakness since the age of eight. She was found to have albuminuria, glycosuria, aminoaciduria and hypophosphatemia. X-ray films revealed multiple pseudofractures of ribs and fibula, generalized demineralization of the bones and rachitic changes of the ends of the long bones. The weakness gradually decreased and her gait slowly improved on a regimen of massive doses of vitamin D₂.

CASE XVII. (Hiatt.²⁸) A thirty-eight year old housewife was examined in 1951 because of progressive pains in her hips, legs and back since the age of nineteen, and limping and waddling since the age of thirty-three. She had gross kyphoscoliosis, was diminutive in appearance and had generalized bone tenderness. X-ray films showed osteomalacia and multiple pseudofractures of her ribs, scapula, pelvis and fibula.

TABLE I
SUMMARY OF CLINICAL DATA ON EIGHTEEN PATIENTS WITH ADULT FANCONI SYNDROME

Case	Age (yr.)			Known Duration of Symptoms (yr.)	Bone Pain	Disturbance in Gait	Weakness	Positive Family History	Rickets in Childhood	Bony Tenderness	Bony Deformity	Bony Rarefaction on X-ray	Fractures and Pseudo-fractures
	Onset	Seen	Followed										
i. Milkman ^{10,11}	38	43	45*	7	yes	waddling	yes	yes	...	yes	yes
ii. Fletcher ¹⁵	31	34	35	4	yes	waddling	not mentioned	yes	...	yes	yes
iii. Hunter ¹⁶	25	29	33	8	yes	difficult	yes	...	yes	...	yes	yes	yes
iv. Edeiken ¹⁷	30	34	34	4	yes	waddling	yes	yes	yes	yes
v. Cooke ⁸	26	36	39*	13	yes	waddling	yes	yes	yes	yes
vi. Stowers ⁹	30	34	35*	5	yes	waddling	yes	yes	yes	...	yes	yes	yes
vii. Linder ¹⁸	8	13	15	7	not mentioned	not mentioned	not mentioned	yes	yes	...	yes	yes	yes
viii. Dent ¹⁹	34	41	41	7	yes	difficult	not mentioned	yes	...	yes	...	yes	yes
ix. Lambert ²⁰	48	56	57	9	yes	unable to walk	yes	yes	yes
x. Anderson ²¹	32	44	45	13	yes	unable to walk	not mentioned	...	yes	...	yes	yes	yes
xi. Milne ²²	48	51	51	3	yes	unable to walk	yes	yes	...	yes	yes
xii. Dragstedt ²³	38	46	47	9	yes	limping	yes	yes	...	no	yes
xiii. Sirota ²⁴	47	50	56	9	yes	waddling	yes	yes	...	yes	yes
xiv. Brick, ²⁵ Kyle ²⁶	33	36	42	9	yes	waddling	not mentioned	yes	...	yes	yes
xv. Salassa ²⁷	7	16	16	9	yes	used crutches	yes	...	yes	yes	yes	yes	yes
xvi. Salassa ²⁷	8	11	12	4	not mentioned	unable to walk	yes	...	yes	...	yes	yes	yes
xvii. Hiatt ²⁸	19	38	41	22	yes	waddling	yes	yes	yes	yes	yes
xviii. Engle ¹	35	38	41*	6	yes	waddling	yes	yes	yes	yes	yes

* Patients died while under observation.

The patient manifested hypophosphatemia, slightly elevated alkaline phosphatase and renal glycosuria. On massive doses of vitamin D₂, 150,000 units a day, strontium lactate 6.3 gm. a day, and a high calcium diet, her electrolytes changed toward normal, bone pain subsided and she was able to walk without a limp; the x-ray films showed healing of fractures with callus formation and increased mineralization of the bones.

CASE XVIII. See preceding article (Engle¹).

REVIEW OF CLINICAL DATA

Table I summarizes clinical data in the eighteen reported cases of adult Fanconi syndrome.

There was no sex predilection among adult patients with Fanconi syndrome, eight women and ten men. No particular occupation or profession was favored. The age of onset of symptoms varied between seven and forty-eight years, with an average of thirty. The onset was insidious in most cases; in Case x it was preceded by acute trauma. The known duration of symptoms varied between three and twenty-two years with a median of eight years. Four patients with adult Fanconi syndrome died while under observa-

tion; the duration of symptoms in these cases was five, six, thirteen and seventeen years.

The most prominent and frequent symptom was bone pain; it was present in sixteen of eighteen patients and involved the lower part of the back, the hips, thighs, legs and, less frequently, the thorax and ribs. In most instances this pain was first noted on arising from a supine, sitting or kneeling position and was aggravated by motion and walking or excessive fatigue. Pain was frequently cramp-like in nature, sometimes dull and constant; eventually it became excruciating and incapacitating. The gait became awkward and hesitant and resembled a duck waddle. Locomotion soon became impossible without the aid of crutches. Eventually most patients became bedridden. Weakness was a prominent complaint. In Case ix it was due to involvement of the pyramidal tract secondary to vertebral collapse. In two patients, Cases xiii and xviii, it was in part due to anemia. In other cases the weakness may have been due to electrolyte abnormalities. Three patients had positive family histories of gross bony deformities, bone fractures, aminoaciduria, renal glycosuria,

albuminuria and hypophosphatemia in various combinations in the members of their families. There was no history of consanguinity in any of the eighteen cases of the adult Fanconi syndrome although consanguinity had been noted in the childhood form by Fanconi^{5,6} and McCune.²⁹ Six patients of eighteen had a history or evidence of rickets in childhood, which may be an indication that the disease process had begun long before any symptoms were recognized.

On physical examination ten patients had bony tenderness somewhere in the back, thighs or ribs, and ten had gross bony deformities ranging from kyphoscoliosis and sternal deformities to gross rachitic changes and dwarfism. One patient¹ had hepatosplenomegaly, probably a manifestation of multiple myeloma. Another patient, Case VII, had hepatomegaly; this was the man who at postmortem examination was found to have a hepatoma. It is of interest that hepatomegaly is a more common finding in the childhood form; it was present in four of fourteen cases in Bickel's series.⁷ Dent explained hepatic dysfunction in these cases as secondary to the chronic loss of amino acids by the kidney.¹³ There was no hypertension noted in any of the reported patients. No cystine storage was demonstrated in any adult case of Fanconi syndrome during life or in four studied postmortem.

Roentgenograms on all reported patients almost invariably showed these two prominent findings: (a) Multiple areas of fractures and pseudofractures of the ribs, pelvis, femurs and vertebrae. These were usually circular bands of diminished density which began in the cortex and then extended across the bone, seemingly severing the continuity, with little or no callus formation. These areas were correlated on postmortem examination with areas of calcium deficiency and increased vascularity and were thought by Milkman¹¹ to be due to pressure of pulsating arteries on the softened bone. (b) Generalized and patchy diminution in the density of bones, variably called osteoporosis, osteomalacia or simply "rarefaction" as the nature of the disorder could not be determined roentgenographically. No significant rarefaction was seen on roentgenograms in Dragstedt's patient (Case XII) even though pseudofractures were prominent. It seems that early in this disease pseudofractures may precede the appearance of recognizable osteomalacia.¹²

No true punched-out areas were seen in seventeen cases, including a patient with multiple

myeloma, Case XIII. In a patient with multiple myeloma, Case XVIII, punched-out areas were seen late in the disease. Of interest are "patchy areas of thinning in the outer table of the skull" described in three other cases; no reproductions of the roentgenograms were found in the papers and a thorough evaluation of these findings was impossible. However localized lesions in the skull have not been described in osteomalacia. It seems, therefore, that coexistence of another condition such as multiple myeloma had not been ruled out with certainty in these cases.

Table II summarizes the biochemical data on the eighteen reported cases of the adult Fanconi syndrome. Marked aminoaciduria was the usual finding, and when quantitatively measured as urinary alpha amino nitrogen it was found to be increased to 550 mg. to 2500 mg. per twenty-four hours (normal is from 200 to 550 mg. per twenty-four hours). The alpha amino nitrogen levels in plasma, however, were never elevated; they were either in the normal range (normal range 4.0 to 7.0 mg. per cent) or low (2.6 to 2.9 mg. per cent). This relationship points to a renal etiology of the aminoaciduria.

All eighteen patients had glycosuria; ketonuria was occasionally present in four patients. It is important to recognize the low renal threshold for acetoacetic acid, since the presence of acetone bodies in the urine may lead to an erroneous conclusion that the glycosuria is diabetic in origin, and giving the patient insulin may precipitate serious hypokalemia.²² The fasting blood sugar was within the normal range in all patients. The glucose tolerance test was entirely normal in ten patients. In four patients the glucose tolerance tests were sometimes mildly diabetic, and glucose was present in all urine specimens. The maximal renal reabsorption of glucose (Tm_G) was measured and found to be decreased in three patients.

The serum phosphorus was consistently low (0.9 to 2.8 mg. per cent) in sixteen patients. In two patients there were variations in the serum phosphorus levels related to transient azotemia. Phosphorus excretion in the urine was demonstrated to be increased in eleven of twelve patients. The maximal tubular reabsorption of phosphorus (Tm_P) was measured in three patients and found to be decreased. It is believed that chronic renal loss of phosphate due to the specific renal defect is the cause of the rickets or osteomalacia which forms so striking a part of the syndrome.^{26,28}

Serum potassium was slightly decreased in

TABLE II
SUMMARY OF LABORATORY DATA ON EIGHTEEN PATIENTS
WITH THE ADULT FANCONI SYNDROME

Laboratory Test	Number of Patients Examined	Result
Aminoaciduria	13	Increased in all
Alpha-amino nitrogen level in plasma	9	Normal in 7, low in 2
Glycosuria	18	Constant in 13, intermittent in 5
Ketonuria	15	Occasionally present in 4
Fasting blood sugar	17	Normal in all
Glucose tolerance test	14	Normal in 10, mild inconstant abnormality in 4
Maximal renal reabsorption of glucose (TmG)	3	Decreased in 3
Serum phosphorus	18	Consistently low in 16, variable in 2
Urinary phosphorus excretion	12	Increased in 11, normal in 1
Maximal tubular reabsorption of phosphorus (TmP)	3	Diminished in 3
Serum potassium	8	Normal in 4, decreased in 4
Serum uric acid	6	Low in 3, normal in 3
Serum calcium	18	Normal in 15, slightly decreased in 3
Serum alkaline phosphatase	17	Elevated in all
Serum CO ₂ content	16	Decreased in 14, normal in 2
Renal glomerular function	17	Normal in 12, slightly impaired in 5
Renal tubular functions	14	Diminished in 14
Proteinuria	17	Present in 11
Bence-Jones proteinuria	9	Present in 2
Serum protein studies	11	Myeloma peak in 1, hypogammaglobulinemia 1, non-specific globulin abnormalities 2; normal serum albumin and globulin in remainder
Anemia	14	Present in 3
Bone marrow examination	5	Plasmacytosis in 2

four patients, with confirmatory changes in the electrocardiogram. The renal loss of potassium

may at times produce hypokalemia and episodes of muscular weakness in this disease. Serum uric acid values were low in three patients (1.4 to 1.7 gm. per cent) and normal in three patients. Serum calcium was normal in fifteen patients with an occasional high normal value; in three patients it was slightly decreased. Serum alkaline phosphatase was elevated in seventeen patients. The serum carbon dioxide content was decreased in fourteen patients. Serum pH was below 7.35 in four patients and above 7.35 in three patients. Urinary pH was above 6.0 in seven patients, below 6.0 in three patients. Serum chloride was normal in nine patients and slightly elevated in four.

Glomerular function as measured variously by blood urea nitrogen, urea clearance and inulin clearance was normal in twelve patients and slightly impaired in five. Nitrogen retention evidently may occur in the terminal stage of this disease. Tubular function, as measured variously by the ability of the kidney to produce concentrated urine, to reabsorb phosphorus, glucose, bicarbonate, potassium, to form ammonia and to excrete phenolsulfonphthalein, was diminished in all fourteen patients tested. Eleven patients excreted protein in the urine, in two of these the protein proved to have Bence-Jones protein characteristics.

In eleven patients serum protein determinations were made. In seven the total protein, albumin and globulin were normal; in one the globulin was elevated to 3.5 gm. per cent with albumin of 4.2 gm. per cent but an electrophoretic study was not made. In one patient an increased alpha₂ fraction and decreased gamma globulin fraction were noted (a non-specific pattern occurring in many chronic and malignant diseases). In a patient with multiple myeloma, Case XIII, a peak was noted in the slow gamma region. In one patient, Case XVIII there was marked hypogammaglobulinemia.

Anemia was not present in eleven patients, was very slight in one and marked in two (Cases XIII and XVIII). No plasmacytosis was noted in the peripheral blood in any patient except one, Case XVIII. Examinations of bone marrow were made in five patients; plasmacytosis was encountered only in two patients (Cases XIII and XVIII). No intracellular inclusions were noted in any of the bone marrow cells except in those of one patient, Case XVIII.

In summary, the Fanconi syndrome in the adult consists of osteomalacia with multiple

fractures and pseudofractures, hypophosphatemia with hyperphosphaturia, slightly elevated alkaline phosphatase, massive aminoaciduria with a normal plasma amino acid level, renal glycosuria; frequently there is albuminuria, alkaline urine, mild systemic acidosis, occasional hypokalemia and hypouricemia. Proximal renal tubule functions are impaired, glomerular filtration is normal or slightly diminished.

PATHOLOGY AND ETIOLOGY

Clay et al.³⁰ made painstaking microdissections of the individual nephrons in two cases of Fanconi syndrome and found consistently that the proximal convoluted tubule was shorter than normal and was joined to the glomerulus by a narrow "swan-like" neck. This observation seems to pinpoint the primary lesion of the Fanconi syndrome to the proximal convoluted tubules of the kidney.

In addition, two independent groups^{8,9} studied the kidney of patients with adult Fanconi syndrome by means of histopathologic technics and both demonstrated absence of alkaline phosphatase from what they felt were proximal tubules, a region usually rich in this enzyme. However this change alone is non-specific and occurs in a number of conditions associated with degeneration of the tubules.³¹

The finding of a crystal-like material within the epithelial cells of the convoluted tubules in one patient, Case XVIII, has added further evidence that the convoluted tubule of the kidney is the site of the lesion in the adult Fanconi syndrome.

There is no agreement on the nature of the anomaly. Some observers^{7,9,32} are impressed by familial occurrence in children and by occasionally positive family history of patients with adult Fanconi syndrome when siblings manifest one or two components of the syndrome. Stowers⁹ postulates a simple hereditary transmission; in individuals homozygous with respect to the trait typical Fanconi disease developing in childhood, with cystine storage, in individuals classifiable as heterozygous the Fanconi syndrome developing in adult life. Dent¹⁹ believes that a simple recessive gene is involved.

Undoubtedly in some of the cases the adult Fanconi syndrome is hereditary. In this category belong the cases in which an unequivocally positive family history has been obtained: Cases VI, VII and VIII. It is important that the urine

of relatives of the patient be examined for aminoaciduria as the most reliable means available at present to rule out the Fanconi syndrome in its mildest or "incomplete" form.

The "transition" form of Fanconi syndrome is probably also hereditary. We apply this term to the patients in whom the first symptoms occurred in late childhood: Cases VII, XV and XVI. These individuals may live long enough to require medical attention as adults. Cystine storage is usually absent and the clinical picture is transitional between adult and childhood forms. Rachitic changes and deformities of the bone are more frequently seen in the childhood form, acidosis and polyuria are more severe, and children are subject to temperature lability with curious febrile attacks and episodes of muscular weakness. Adults, on the other hand, manifest less systemic disturbances, show no cystinosis, but have more bone pain and tenderness with the pseudofractures. It is expected that with the current application of the principles of electrolyte control in the children with Fanconi disease many may live through puberty and the "transition" group will increase in number.

Exclusive of patients with clearcut family history and the "transition" cases, which account for five of the eighteen that were reviewed, there still remain a number of adult patients with Fanconi syndrome in whom heredity cannot be implicated. With expansion of our knowledge about the mechanisms of secondary renal aminoaciduria (Table III), a strong possibility exists that some of the adult patients with Fanconi syndrome derive this disturbance secondary to some other factor or disease.

Aminoaciduria associated with a normal plasma level of amino acids is a well known finding in Wilson's disease.^{33,34} Cooper et al.³⁵ observed not only aminoaciduria but also renal glycosuria in three of six patients with Wilson's disease. Another patient had derangement of calcium and phosphorus metabolism and osteomalacia. These authors postulated damage to the proximal renal tubules by copper deposits as an explanation of this phenomenon.

Van Creveld^{36,37} reported a most interesting case wherein a seventeen month old child received large doses of vitamin D₂ given for a year and rickets, renal glycosuria, albuminuria, aminoaciduria and phosphaturia developed. Cessation of the vitamin D therapy, to which the child was considered hypersensitive, led to alleviation of the condition. The author be-

TABLE III
CAUSES OF AMINOACIDURIA*

- A. PRERENAL—associated with aminoacidemia, "overflow" aminoaciduria
1. Failure to utilize dietary amino acids for protein synthesis
Certain steatorrheas, especially celiac disease in children
 2. Failure of liver to deaminate amino acids
Acute yellow atrophy with generalized aminoaciduria
Chronic liver disease with "hepatic cystinuria"
Postanesthesia transitory cystinuria
Galactosemia
Transient physiologic aminoaciduria of the newborn
 3. Increased protein catabolism
Progressive muscular dystrophy, cortisone and ACTH therapy, hyperthyroidism, widespread cancer, extensive burns and crush injuries
 4. Metabolic disorders affecting special amino acids
Phenylketonuria (phenylpyruvic oligophrenia), tyrosinosis
Alkaptonuria
- B. RENAL TUBULAR DEFECT—no aminoacidemia
1. Primary cystine-lysinuria (benign hereditary specific renal tubular defect for 4 amino acids: cystine, lysine, arginine and ornithin)
 2. Primary aminoaciduria
Lignac-Fanconi disease in children: ? hereditary absence of phosphatase from the proximal convoluted tubule, producing generalized aminoaciduria, glycosuria, acidosis, hypophosphatemia, rickets and dwarfism with late cystine storage†
Hereditary cases of the adult Fanconi syndrome
 3. Secondary aminoaciduria
Copper deposits in Wilson's disease³⁵
? Vitamin D hypersensitivity in some rachitic patients^{36,37}
Glycogen storage disease³⁹
Lead intoxication⁴⁰
Lysol burn and poisoning⁴¹
Uranium poisoning⁴²
? Cadmium toxicity^{43,44}
? Bismuth toxicity⁴⁵
Experimental maleic acid toxicity⁴⁶
? Bence-Jones protein deposits in multiple myeloma^{1,24}
Secondary adult Fanconi syndrome, cause unknown

* Additional references for the listed conditions may be found in Brick⁵⁶ and Bickel.⁷

† Some believe that Lignac-Fanconi disease in children is due to an inborn error in the metabolism of amino acids with resulting storage of cystine and overflow of this and other amino acids in the urine.

lieved that this transitory Fanconi syndrome was caused by the effect of the vitamin D on the renal tubules. Rabbits fed excessive doses of calciferol do, indeed, develop intrarenal

microscopic calcium deposits and tubular degeneration.³⁸

Fanconi and Bickel³⁹ noted the syndrome of aminoaciduria without aminoacidemia, of renal glycosuria, polyuria, phosphaturia, albuminuria, alkaline urine, hypophosphatemia, mild systemic acidosis, rickets and dwarfism in a child with glycogen storage disease and felt that this syndrome was due to the damage of the proximal renal tubules by the glycogen deposits in the kidney.

Wilson and Dent⁴⁰ reported the occurrence of renal glycosuria, albuminuria and aminoaciduria in chronic lead intoxication in children, presumably secondary to damage to the tubules by the metal while it was being excreted by the kidney.

Renal glycosuria and aminoaciduria in the face of a normal plasma amino nitrogen level were reported in a case of a severe lysol burn in a laboratory assistant as a probable manifestation of gross tubular dysfunction during the early diuretic phase. These changes were reversible.⁴¹

Uranium is recognized as another potent nephrotoxic agent which acts on the proximal convoluted tubules. Experimental uranium poisoning in rabbits results in marked aminoaciduria and albuminuria, among other defects.⁴²

Nicaud⁴³ and Lafitte⁴⁴ reported six cases of typical Milkman syndrome with bony rarefaction and "pseudofractures," hypophosphatemia and increased alkaline phosphatase among cadmium workers. No studies of aminoaciduria were conducted in these cases. Bismuth is another metal which has been implicated in causing "osteoporosis" in a vigorously treated syphilitic patient.⁴⁵

Harrison and Harrison⁴⁶ produced renal glycosuria, phosphaturia and aminoaciduria in rats by injection of maleic acid intraperitoneally and postulated damage to the proximal tubules by that agent as an explanation for this transient Fanconi syndrome.

Damage to the kidney by endogenous degradation products of protein has long been suspected by Zollinger,⁴⁷ who described a chronic interstitial nephritis of disorders of protein metabolism in cases of multiple myeloma, lipid nephrosis, amyloidosis and gout. These patients were not sufficiently studied clinically to ascertain the presence of a Fanconi syndrome.

It seems, therefore, that there are a number of agents and conditions which can damage the

proximal renal tubules, resulting in a partial or complete Fanconi syndrome. From the reports available, it is difficult to point out the responsible agent in each of the reviewed cases. However several possibilities become apparent. One patient, Case XII, had received massive anti-syphilitic treatment in the form of bismuth; although in usual clinical doses bismuth seems to be harmless, osteoporosis due to bismuth has been reported.⁴⁵ It is of interest that two of the patients, Cases XIII and XVIII, had associated multiple myeloma with marked Bence-Jones proteinuria. It is quite possible that prolonged Bence-Jones proteinuria with deposits within the renal tubular cells results in a reabsorption defect identical with that in the Fanconi syndrome. The finding of the crystal-like material within the epithelial cells of the convoluted tubules in a patient, Case XVIII, supported this hypothesis.¹

Even though there are a number of agents known to cause a partial or complete renal tubular reabsorption defect, this action must be fairly specific in such instances since patients with diffuse renal disease and considerable renal damage do not exhibit excessive aminoaciduria.⁴⁸ Predominance of heavy metals on the list of causative agents associated with this reabsorption defect and the report by Clarkson and Kench⁴⁹ of increased amino acid excretion by men absorbing heavy metals further points up a certain degree of specificity.

A review of available evidence indicates that the adult Fanconi syndrome includes primary cases of a hereditary defect in tubular reabsorption, and secondary cases in which the defect resulted as a complication of an underlying process. The responsible agent in the secondary cases can be either a space-occupying deposit in the proximal convoluted tubular cells or a chemical toxin affecting the reabsorption processes.

It is expected that with more frequent clinical application of paper chromatography technics, more cases will be detected and that a wider spectrum of causative agents will become known.

It is also suggested that many cases reported under "Milkman's syndrome"^{50,51} and "Vitamin D resistant rickets"^{52,53} may be related to the adult Fanconi syndrome. In the spectrum of the functions of the proximal convoluted tubules, few or all may be affected in any particular case. Hyperphosphaturia with resulting osteomalacia

and apparent "vitamin D resistance" may be the only manifestation in the "mild case," while on the other side of the scale, additional glycosuria, aminoaciduria, polyuria and hyperkaliuria constitute an advanced case.³² Furthermore, it is suspected that if studied for aminoaciduria and other metabolic derangements, some of the so-called "vitamin D resistant osteomalacias" with a radiologic Milkman's syndrome will be found to have involvement of other functions of the proximal tubules.

TREATMENT

Most of the patients on record have been treated with vitamin D₂ at one time or another and have been found "resistant" in the sense that their symptoms and bone changes were not affected by conventional doses. In some, benefit was achieved by massive vitamin D₂ doses (100,000 units and more per day) along with a nutritious diet high in calcium. The patients showed relief of pain and the x-ray films revealed remineralization and healing of fractures.^{18,20,27,28} Hiatt et al.²⁸ add strontium lactate, 6.3 gm. a day, to the regimen. Dent³² recommends administering an initial dose of 50,000 units of vitamin D and increasing it gradually in an attempt to raise the serum phosphorus level to normal. The lowest maintenance dose is then attained. Some individuals may require as much as 500,000 units a day. The serum calcium level should be determined every two to six weeks and the drug discontinued if the serum calcium exceeds 11.5 mg. per cent or if the patient complains of decreased appetite, nausea, polyuria and dysuria. Dragstedt,²³ on the other hand, recommends using the serum alkaline phosphatase determination as an indicator of vitamin D overdosage. He feels that administration of the vitamin should be discontinued as soon as the serum alkaline phosphatase returns to normal.

An important aspect of treatment is correction of an existing electrolyte imbalance. Shohl's alkalinizing mixture, which contains 140 gm. of citric acid and 98 gm. of sodium citrate in 1 L. of water, is recommended by Albright¹² and was used successfully by Anderson²¹ and Sirota²⁴ for correcting systemic acidosis. The patient drank 30 cc. of this mixture three times a day with restoration of normal electrolyte balance, recalcification of bones and healing of fractures. Metabolic studies indicated that a high intake of calcium and phosphorus potentiate the effects

of Shohl's regimen. The alkalinizing mixture should be continued indefinitely with the aim of maintaining serum carbon dioxide content at 25 to 27 mM/L. Oral administration of citric acid should also facilitate calcium absorption by increasing the acidity of the intestinal contents.¹²

Modification of this alkalinizing regimen may be accomplished by addition of potassium citrate for those who also manifest hypopotassemia.²² A corrective solution may contain 140 gm. of citric acid, 75 gm. of sodium citrate and 25 gm. of potassium citrate in 1 L. of water. The patient ingests 30 cc. of the mixture five times a day. Milne's patient had a most remarkable recovery following a month of this alkalinizing regimen, plus calcium lactate, 8 gm. and calciferol, 150,000 units a day. The patient was able to walk without pain, the bony tenderness disappeared, pseudofractures healed, and the serum electrolytes returned to normal.²²

A further refinement of the regimen, first introduced by Anderson,²¹ is the addition of sex hormones, especially testosterone. The theoretic reason for the use of sex hormones in the adult Fanconi syndrome is their known effect on any secondary osteoporosis by way of inducing a positive nitrogen, calcium and phosphorus balance.⁵⁴ Methyl testosterone, in addition, has been demonstrated to have a renal effect, inducing hyperplasia of renal tubules in animals.⁵⁵ Its renal effect in humans is not so well defined. In Anderson's case²¹ it was used in doses of 25 mg. of oral methyl testosterone daily and was found to be followed by a decrease in amino acid excretion in the urine as well as by subjective improvement in the patient.

Treatment of the adult Fanconi syndrome then, has been aimed at correction of the symptoms by high calcium, high phosphorus and strontium intake, massive vitamin D₂ doses, alkalinization and administration of sex hormones. Definitive treatment should include an attempt to correct the primary cause of the syndrome in each case.

SUMMARY

Eighteen reported cases of the adult Fanconi syndrome are reviewed.

The possible etiology of this syndrome is discussed. Although some cases of adult Fanconi syndrome are undoubtedly of hereditary nature, others may result from acquired kidney lesions in a number of disease processes.

Forms of therapy currently in use are mentioned.

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Glycoproteins in Serum from Patients with Myeloma, Macroglobulinemia and Related Conditions*

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MORE or less chronic conditions characterized by a markedly abnormal (quantitative and/or qualitative) serum protein pattern have been designated "dysproteinemias." The correlation between different clinical pictures of dysproteinemia and various physicochemical or chemical characteristics of the abnormally increased protein fractions is not only of academic interest but also of practical diagnostic and prognostic value. As yet no single laboratory method is available for differentiation of the various types of dysproteinemia. However the relatively simple method of quantitative protein electrophoresis will yield data possibly permitting a better classification of the dysproteinemias.

In one of the two main types of dysproteinemia the electrophoretic diagram usually shows a characteristic *narrow* peak (band) somewhere in the β - γ region.¹ The shape of the peak (band) suggests that, of the many individual serum proteins in the β - γ region, only one, or at most a few, occurs in increased concentration. This type of diagram is seen in systemic diseases such as multiple myeloma, macroglobulinemia, certain rare instances of "reticulosis" or lymphatic leukemia, and sometimes in the absence of any known symptoms.

The other group is also characterized by an increase of β or γ globulins but here the peaks or bands are wider than those seen in the "systemic" diseases. This greater width implies an increased concentration of at least several individual proteins with isoelectric points close to a value corresponding to the top of the peak. The peaks (bands) vary in width; they may cover only half the normal γ region or the entire γ

region and part of the β_2 region. This type of diagram is seen in such diseases as chronic protozoal, bacterial and viral infections, collagen diseases, hyper-immune states and "essential" hyperglobulinemias (Waldenström and others). The electrophoretic and ultracentrifugal behavior of the pathologic γ -globulin in a chronic viral disease (lymphogranuloma venereum) with this type of increase was studied by Pedersen, Sonck and Waldenström.²

The appearances of the electrophoretic protein patterns in these two types of dysproteinemias are illustrated in Figure 1.

The present paper is concerned with the electrophoretic protein and carbohydrate distribution in serums from patients belonging to the first type, the systemic diseases. During the last decade interest in plasma glycoproteins has been concentrated mainly on the α -globulin fractions (Werner,³ Winzler,⁴ Schultze et al.,⁵ Greenspan⁶), since the main part of the normal glycoproteins belong to this electrophoretic protein group and the bulk of normal γ -globulins are known to contain only 1 to 2 per cent carbohydrate when estimated as galactomanoside. These figures were obtained when γ -globulins were analyzed after isolation by preparative boundary electrophoresis, convection electrophoretic technics, or by precipitation with salts or ethanol under standardized conditions. The two last methods were used by Hillman and Lohss^{7,8} and Smith et al.⁹ to isolate the abnormal components of serums from patients with multiple myeloma. They studied the purified proteins in detail by several chemical, physicochemical and immunochemical methods.

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Since the pioneer work of Lohss and Hillman^{7,8} does not seem to have received the attention it deserves, their carbohydrate determinations are given together with those of Smith *et al.*⁹ in Table 1. Both groups of investigators found a higher carbohydrate content of some of the β and

TABLE 1
HEXOSE CONTENT*

	Normal γ	Varying Mobility γ	β_2	β_1	α_2
Lohss <i>et al.</i> ⁸	2.2-2.9	1.5-2.5 (6 cases)	2.7, 4.0, 3.6	3.8	3.4
Smith <i>et al.</i> ⁹		0.83, 1.11, 1.59		3.1	

* On analysis of "abnormal" serum protein components with varying electrophoretic mobility isolated from different myeloma serums.

α myeloma serums than of the γ myeloma serums.

A new, simple approach to semi-quantitative estimation of carbohydrate distribution among the serum proteins was inaugurated by Kōiw and Grönwall.¹⁰ They combined electrophoresis in a filter paper medium with a histochemical method for coloration of carbohydrates (oxidation of the glycoproteins with periodic acid followed by staining with Schiff's reagent). This periodic acid-Schiff method has since been modified and used by several research workers in investigating the pattern of glycoproteins in different dysproteinemias such as the systemic diseases.

The densitometric technic was regularly used to evaluate the color of the paper strips obtained after electrophoretic separation and staining of the carbohydrates. Diagrams showing that the carbohydrate content of the pathologic fraction in myeloma serums varies from one patient to another have been published by several authors¹¹⁻¹⁴ and in macroglobulinemia a relatively strong Schiff color has been observed.^{11,15,16} In the estimation of the carbohydrate content of the abnormal component preparative zone electrophoresis on paper was used in a few cases of myeloma by Sonnet¹⁶ and Olhagen¹⁷ and in one case by Goa.¹⁸

An increased concentration of hexoses and hexosamine in the serum from patients with "multiple myeloma" has also been found by

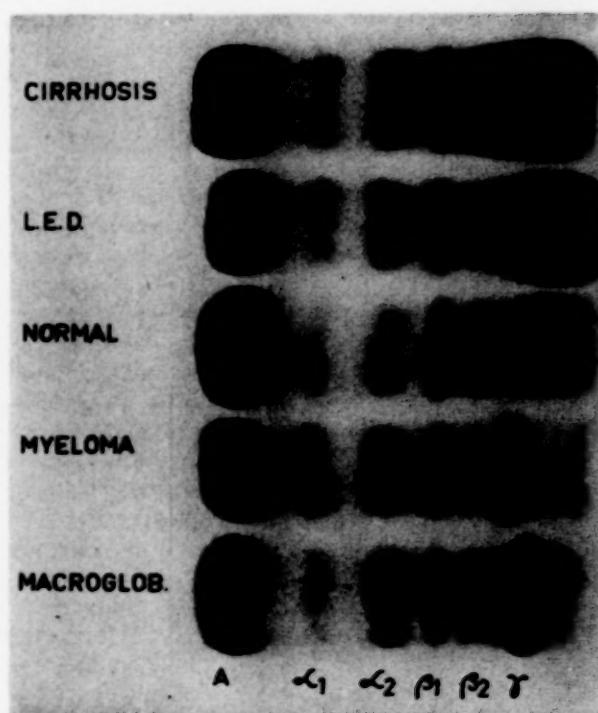


FIG. 1. The electrophoretic appearance of the γ -globulin fraction in different types of "dysproteinemia."

Greenspan,¹⁹ Sachs,¹⁴ Rice,¹² Sonnet¹⁶ and Smith.⁹ Several authors^{15,16,20-22} who have analyzed one or two serums each from patients with macroglobulinemia found a high serum content of hexose and hexosamine. The periodic acid-Schiff color of the abnormal component was also found to be intense. Sonnet¹⁶ showed a markedly increased fucose concentration in the pathologic serum fractions from a few patients with systemic diseases.

Di Guglielmo *et al.*^{20,21} therefore expressed the opinion that a high polysaccharide content might possibly distinguish the macroglobulins in macroglobulinemia from the abnormal proteins in myeloma. The material hitherto available has, however, been insufficient for valid conclusions on this point since relatively high concentrations of carbohydrates have also sometimes been found in myeloma serums.

EXPERIMENTAL DATA

Material: All the serums used have been stored at -15°C . usually for one month to two years.

Methods: Moving boundary electrophoresis according to Svensson.²³

Quantitative paper electrophoresis according to Laurell, Laurell and Skoog.²⁴ The buffer used contained calcium ions. This results in a splitting of the β -fraction into two fractions with different electrophoretic mobilities. The fraction with higher mobility was

called β_1 and the one with lower mobility was called β_2^{Ca} .

Serum protein concentration according to Kjeldahl.

Protein-bound hexose (anthrone reagent) according to v. Holt,²⁵ who states that this procedure only determines mannose and galactose but we found interference by fucose. The product obtained from the reaction between fucose and anthrone gives, under the same conditions, approximately the same specific extinction as the reaction product from mannose-galactose (1:1). We made separate determinations of the fucose content of the different serums. It would have been possible to calculate the values for true hexose from the values obtained for "protein-bound hexoses" and fucose. This was not done because we were not convinced of the reliability of the fucose values, and because most other authors give their values for protein-bound hexoses without correction for the presence of fucose.

Protein-bound hexosamine according to a modification of Elson and Morgan's^{26a,b} method.

Protein-bound fucose according to Winzler's⁴ modification of Dische and Shettles' method.²⁷ Our normal values agreed with those of Winzler but a critical analysis of the method suggested that the fucose values obtained with Winzler's method can be accepted only as a rough semi-quantitative expression of the fucose content of serums when protein-bound hexoses occur in widely varying concentration.

Sialic acid according to Werner and Odin.²⁸ The method has been adapted for serum analyses and is therefore presented in detail.

Dilute 0.50 ml. serum (constriction pipette) with 1.0 ml. NaCl (0.85 per cent). Discharge 0.5 ml. of this dilution into 10 ml. alcohol with the aid of a constriction pipette. Mix at once. Centrifuge. Decant the supernatant. Immediately add 5 ml. NaCl (0.85 per cent) and shake the tube as soon as possible to dissolve the precipitate. Centrifuge. Transfer 4 ml. of the solution to a centrifuge tube with a ground-glass stopper and mix with 3 ml. of the orcinol reagent (v. seq.) and 0.2 ml. $FeCl_3$ solution. Heat the tubes for exactly ten minutes at $108^\circ C. \pm 0.2^\circ$ and then cool under running tap water; add 4 ml. redistilled amyl alcohol (see Werner and Odin²⁸). Shake. Centrifuge. Read the upper layer at 570 $m\mu$ against a blank obtained by replacing the serum by water. The standard curve was constructed with the aid of pure sialic acid.*

The orcinol reagent is prepared as follows: Dissolve 375 mg. orcinol (Eastman) and dilute to 200 ml. with dilute HCl (200 ml. conc. HCl + 50 ml. distilled H_2O). The ferric chloride solution is prepared as follows: Dissolve and dilute 90 mg. $FeCl_3 \cdot 6 H_2O$ to 25 ml. with diluted HCl (200 ml. conc. HCl + 50 ml. distilled H_2O).

Electrophoretic polysaccharide (periodic acid-Schiff) pattern: After electrophoretic separation, stain the filter

* The sialic acid was supplied by Dr. L. Odin.

papers according to Björnesjö²⁹ (modified by Laurell and Skoog³⁰). Elute the dye and determine the percentage of the color in the various electrophoretic protein fractions.

Euglobulin test with distilled water, "water dilution test." (Sia.³¹) Pipette one drop of serum onto the surface of the distilled water in a cylinder about 25 cm. high. A more or less pronounced cloudiness may be seen in different pathologic and normal serums. In the present investigation the test was judged to be positive only when a massive precipitate appeared immediately and settled rapidly to the bottom of the vessel without formation of any diffuse cloudiness behind the sedimenting floccules. The precipitate is readily soluble in normal saline solution.

Ultracentrifugation was performed by K. O. Pedersen.

Terminology: Proteins with a mobility less than that of the bulk of the normal γ -globulins (γ_2) were designated γ_3 (slow γ -globulins). Fractions with a mobility higher than that of γ_2 but lower than that of β_2^{Ca} were termed γ_1 (fast γ -globulins). With the technic employed the proteins of the conventional β -group were separated into two groups (β_2^{Ca} and β_1).*

Two of the abnormal components here designated as β_2^{Ca} components showed, in free electrophoresis, the same mobility as the bulk of the β -globulins. Figure 2 gives typical patterns of "abnormal" proteins of varying mobility, and illustrates the principles of classification. The limits between the groups were arbitrary and the groups overlapped one another. A single component with a mobility value intermediate between those of the β_2^{Ca} and the γ_1 -fractions, for example, was designated a β_2^{Ca} - γ_1 component.

Calculations: The numerical values reported herein are based not only on the analysis effected but also on calculations founded on the following assumptions: (a) that with the technic employed all proteins bind the same amount of bromphenol blue per unit of weight. The values obtained on analysis of serums from apparently healthy individuals, by the staining technic used, agreed fairly well with data hitherto obtained by the moving boundary electrophoresis technic. In spite of this the absolute protein values recorded for the concentration of the "abnormal" component must be regarded as semi-quantitative. (b) that the color obtained in the various electrophoretic paper segments after oxidation and treatment with Schiff's reagent is proportional to the polysaccharide content of the respective segments. This assumption is supported by Björnesjö's²⁹ observations on the stainability of different glycoproteins. He showed that glycoproteins with a polysaccharide moiety of varying composition stain in proportion to the total amount of polysaccharide and not in proportion to any of the individual sugars contained therein

* This separation can be explained mainly by the fact that the electrophoresis buffer used contains calcium ions, which retard the migration of some of the proteins (β_2^{Ca}) belonging to the β -group.

(hexose, hexosamine or sialic acid). No data are available on fucose but since fucose is included in glycoproteins in only low concentration, its reaction in tests using the periodic acid-Schiff technic is not absolutely specific; a quantitative addition of color in one or

TABLE II
ELECTROPHORETIC PROTEIN PATTERN*

Case	Serum Total Pro- tein	Albu- min	α_1	α_2	β	γ	Abnormal Component	
							Mo- bil- ity	Con- cen- tra- tion
Group I. Patients with Myeloma								
1, O. A.	12.25	3.13	0.31	0.39	0.54	7.88	γ_2	7.5
2, K. J.	8.45	3.04	0.46	0.63	0.52	3.80	γ_1	3.3
3, H. H.	11.75	3.63	0.34	0.62	0.65	6.51	γ_2 - γ_1	6.0
4, H. F.	13.04	3.57	0.56	1.06	0.82	7.03	γ_2	6.5
5, A. N.	9.76	3.44	0.29	0.42	0.52	5.09	γ_2	4.6
6, A. J.	11.30	2.19	0.25	0.29	0.40	8.17	γ_2	7.7
7, A. L.	8.44	3.62	0.38	0.58	0.69	3.17	γ_2	2.7
8, O. K.	11.79	2.46	0.39	0.60	0.65	7.69	γ_1 - γ_2	7.2
9, K. L.	9.89	2.85	0.29	0.45	0.61	6.29	γ_1 - γ_2	5.6
10, A. S.	6.43	3.12	0.59	0.68	0.79	1.25	γ_1	0.8
11, J. B.	9.73	2.89	0.33	0.41	0.46	5.64	β_2 - γ_1	5.3
12, W. J.	8.31	3.53	0.57	0.91	0.66	2.64	β_2 - γ_1	2.0
13, O. H.	9.38	2.57	0.32	0.53	0.50	5.46	β_2 - γ_1	4.7
14, G. L.	9.61	2.71	0.32	0.55	0.55	5.48	β_2 - γ_1	5.0
15, J. C.	8.45	3.06	0.27	0.48	4.14	0.50	β_1 - γ_1	3.6
16, S. N.	9.63	2.41	0.36	0.63	5.73	0.50	β_2 - γ_1	5.0
17, N. J.	8.56	3.88	0.34	0.57	3.23	0.54	β_2 - γ_1	2.5
18, A. H.	11.08	2.64	0.29	0.58	7.17	0.40	β_1 - β_2	6.4
Group II. Patients with Other Diseases								
19, N. W.	8.3	3.73	0.53	0.80	0.75	2.49	γ_2	1.9
20, M. F.	10.16	3.15	0.37	0.50	0.66	5.48	γ_2	5.0
21, S. W.	8.55	3.65	0.43	0.55	0.70	3.22	γ_2	2.6
22, F. F.	9.73	3.31	0.46	0.57	0.63	4.76	γ_2	4.1
23, M. O.	11.35	4.05	0.28	0.40	0.53	6.09	γ_2	5.4
24, N. R.	9.63	3.32	0.38	0.67	0.70	4.57	γ_2	4.0
25, G. M.	9.89	2.15	0.30	0.60	0.61	6.23	γ_2	5.5
26, G. A.	5.84	3.55	0.44	0.47	0.55	0.83	γ_2	0.5
27, E. S.	9.16	3.87	0.34	0.83	0.62	3.30	γ_1 - γ_2	2.6
28, E. P.	7.91	4.46	0.39	0.50	0.85	1.71	γ_1 - γ_2	0.9
29, H. K.	6.60	3.31	0.41	0.52	0.63	1.73	γ_1	0.5
30, M. B.	10.06	3.03	0.26	0.37	0.37	6.03	β_2 - γ_1	5.2
Eighty-five Normal Subjects								
Normal mean value	7.2	4.7	0.35	0.53	0.77	0.89
Standard deviation \pm	0.26	0.3	0.036	0.062	0.093	0.134

* All values are given as gm. protein/100 ml. serum.

more fractions can, for example, be due to the occurrence of unsaturated fatty acids or other reactive lipids. The periodic acid-Schiff values can therefore be used only for semi-quantitative calculations.

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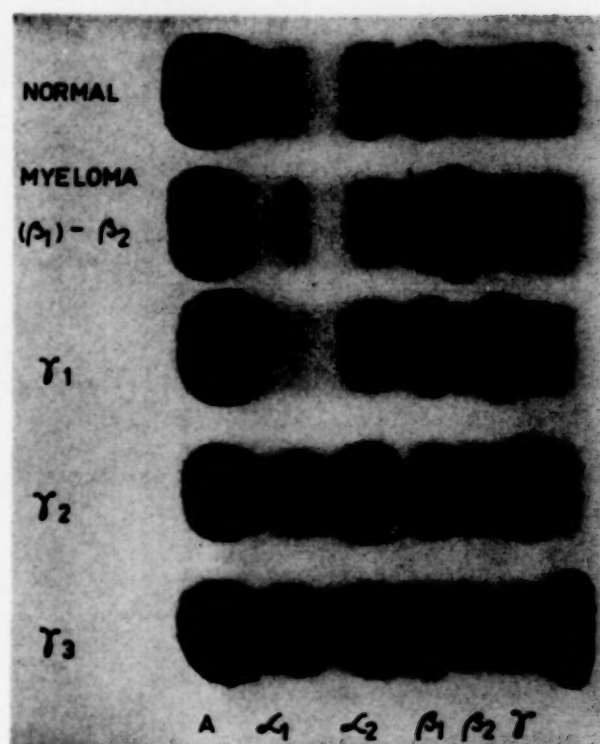


FIG. 2. Examples of serums containing abnormal components with varying mobility.

RESULTS

The results are divided into two main groups: I, Cases 1 to 18, myelomatosis; II, Cases 19 to 30, macroglobulinemia, lymphatic leukemia, etc. Brief case histories are appended.

The results of the serum protein determinations and of the paper electrophoretic fractionations, and the mobility of the abnormal components are given in Table II. In all the tables the patients in both groups are arranged according to the mobility of the pathologic serum protein fraction. The values for all electrophoretic fractions are given for two reasons, first because the albumin and α -values reflect the degree of activity of the pathologic process, and second because the main portion of the normal glycoproteins belong to the α -groups. The latter fact makes it difficult to evaluate the distribution of the glycoproteins in serums containing an abnormal γ - or β -fraction in low concentration. At the bottom of the tables, the normal values obtained on analysis of eighty-five serums from apparently healthy blood donors are given for comparison. The standard deviation embraces the error of the method and the biologic variation. In the last column of Table II the calculated value of the absolute concentration of the ab-

TABLE III
CONCENTRATIONS OF POLYSACCHARIDES
IN UNFRACTIONATED SERUMS*

Case	Hex- ose	Hexos- amine	Fucose	Sialic Acid	Poly- sac- cha- ride†
<i>Group I. Patients with Myeloma</i>					
1, A. O.	244	86	24	81	411
2, K. J.	207	138	21	89	434
3, H. H.	175	190	..	85	450
4, H. F.	195	160	29	66	421
5, A. N.	138	113	12	55	306
6, A. J.	153	130	15	41	324
7, A. L.	128	103	..	72	303
8, O. K.	207	164	..	45	416
9, K. L.	179	137	28	41	357
10, A. S.	138	152	10	71	361
11, J. B.	280	215	..	90	585
12, W. J.	143	103	12	87	333
13, O. H.	285	164	20	137	586
14, G. L.	188	169	23
15, J. C.	201	157	19	79	438
16, S. N.	297	226	35	150	673
17, N. J.	268	138	21	67	473
18, A. H.	357	200	25	91	648
<i>Group II. Patients with Other Diseases</i>					
19, N. W.	243	191	43	102	536
20, M. F.	308	236	..	102	646
21, S. W.	239	209	18	74	522
22, F. F.	312	200	21	72	584
23, M. O.	492	270	39	102	864
24, N. R.	358	184	29	109	651
25, G. M.	410	203	47	107	720
26, G. A.	143	87	13	77	307
27, E. S.	364	213	45	82	659
28, E. P.	132	99	10	72	304
29, H. K.	176	114	22	85	375
30, M. B.	385	218	38	80	683
<i>Normal Subjects</i>					
Normal range of variation	106-132	80-100	6.0-11.2	50-65	..

* All values are given in mg./100 ml. serum.

† The sums of the components with the exclusion of fucose.

normal components is given. This calculation is based on the protein value found in the paper segment containing the abnormal fraction, and from this value we subtracted a visually estimated value for other proteins that had fallen within the segment under consideration. In

those cases in which the abnormal component was predominant, the relative experimental error was small. In those cases, however, in which the abnormal component represented less than half the color of the segment under consideration, only a relatively good approximation was obtained for the concentration of the abnormal component. For values given as 1.0 to 0.6 per cent the error was probably of the order of ± 10 per cent and for lower concentrations ± 20 per cent. The systematic errors caused by the differing stainability of the various proteins with bromphenol blue are not included.

Table III gives the content of protein-bound hexose, hexosamine, fucose and sialic acid in the different serums. At this stage of the investigation these determinations were made only on whole serum and not on isolated electrophoretic components. It is apparent from the data of Table III that the polysaccharide content of the serum from these patients varies between normal and markedly increased levels. On comparison of Tables II and III it is apparent that the degree of increase in the polysaccharides depends on the concentration of the abnormal component, but that no correlation is demonstrable between the values for the concentration of the abnormal protein fraction and the values for the total polysaccharide concentration or that of any of the simple sugar constituents.

The relative distribution of the polysaccharides among the various electrophoretic fractions was determined by analysis of the periodic acid-Schiff-stained filter papers. The relative color distribution among the various fractions which was obtained is, however, of limited interest when the electrophoretic protein pattern is markedly abnormal or when it is desired to compare the carbohydrate content of different electrophoretic components from various serums. The relative values obtained with the periodic acid-Schiff method were therefore converted into absolute values, on the basis of values found for the protein-bound and anthrone-reacting substances in the various serums. (Table V.) These are chiefly galactose and mannose. No correction was made for the methodologic error caused by fucose or tryptophane. Since hexosamine and sialic acid also react with periodic acid-Schiff, the percentages preferably should have been converted to absolute figures on the basis of the total polysaccharide content of the serum. Since our normal, electrophoretically fractionated, serums had been analyzed only for

TABLE IV
RELATIVE CONCENTRATIONS OF POLYSACCHARIDE
CONSTITUENTS*

Case	Hexose	Hexos- amine	Fucose	Sialic Acid
<i>Group I. Patients with Myeloma</i>				
1, A. O.	2	0.8	0.2	0.7
2, K. J.	2	1.5	0.2	1.0
3, H. H.	2	2.4	...	1.0
4, H. F.	2	1.9	0.3	0.8
5, A. N.	2	1.8	0.2	0.9
6, A. J.	2	1.9	0.2	0.6
7, A. L.	2	1.7	...	1.2
8, O. K.	2	1.7	...	0.5
9, K. L.	2	1.8	0.4	0.5
10, A. S.	2	2.4	0.2	1.1
11, J. B.	2	1.5	...	0.6
12, W. J.	2	1.6	0.2	1.3
13, O. H.	2	1.2	0.2	1.0
14, G. L.	2	2.0	0.3	...
15, J. C.	2	1.7	0.2	0.9
16, S. N.	2	1.7	0.3	1.1
17, N. J.	2	1.1	0.2	0.5
18, A. H.	2	1.2	0.2	0.5
<i>Group II. Patients with Other Diseases</i>				
19, N. W.	2	1.6	0.4	0.8
20, M. F.	2	1.5	...	0.7
21, S. W.	2	1.7	...	0.6
22, F. F.	2	1.3	...	0.5
23, M. O.	2	1.2	0.2	0.5
24, N. R.	2	1.1	0.2	0.7
25, G. M.	2	1.1	0.3	0.6
26, G. A.	2	1.3	0.2	1.2
27, E. S.	2	1.3	0.3	0.5
28, E. P.	2	1.6	0.2	1.2
29, H. K.	2	1.5	0.3	1.1
30, M. B.	2	1.3	0.2	0.5
<i>Normal Subjects</i>				
γ -fraction ³⁴	2	1.2	...	0.6
β -fraction ³⁴	2	1.2	...	1.3

* All values are given in arbitrary units; the value found for hexose was set as a standard of 2 units. The analytical values found for the various constituents were divided by half the hexose value in order to obtain the units employed. No allowance was made for differences in molecular weights.

the content of anthrone-reacting substances, we decided to convert the percentages to absolute values in order to obtain suitable figures for comparison. This procedure is acceptable only if the simple sugars (mannose, galactose, hexosamine, fucose and sialic acid) are included in the

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TABLE V
ELECTROPHORETIC DISTRIBUTION OF PROTEIN-BOUND
POLYSACCHARIDES

Case	"Hexoses" in							Per cent of Periodic Acid-Schiff Stain Bound to Pathologic Component
	Total Serum	Albumin	α_1	α_2	β_1	β_2 Ca	γ	
Group I. Patients with Myeloma								
1, A. O.	244	21	57	61		30	74	29
2, K. J.	207	23	50	73		31	31	13
3, H. H.	175	2	23	35		21	94	51
4, H. F.	195	4	35	55		37	64	31
5, A. N.	138	15	28	28		25	43	28
6, A. J.	153	15	12	25		21	80	50
7, A. L.	128	4	27	33		26	38	27
8, O. K.	207	10	39	54		35	69	31
9, K. L.	179	10	32	39		29	69	35
10, A. S.	138	8	43	59		16	12	3
11, J. B.	280	13	29	31	21*		186*	64
12, W. J.	143	17	31	51	22		22	10
13, O. H.	285	3	29	40	31		182	60
14, G. L.	188	30	28	34	27		69	35
15, J. C.	201	4	20	36		111		30
16, S. N.	297	9	24	36	24		204	67
17, N. J.	268	3	46	62		134		23
18, A. H.	357	3	29	36		264		25
Group II. Patients with Other Diseases								
19, N. W.	243	3	31	40		29	140	53
20, M. F.	308	14	33	40		31	190	58
21, S. W.	239	11	23	34		25	145	59
22, F. F.	312	11	26	40		22	214	67
23, M. O.	492	19	34	54		34	351	70
24, N. R.	358	0	43	68		25	222	60
25, G. M.	410	4	33	49		29	295	71
26, G. A.	143	13	32	30		26	43	28
27, E. S.	364	18	22	29		18	277	74
28, E. P.	132	10	22	29		20	51	31
29, H. K.	176	15	33	48		23	57	27
30, M. B.	385	4	26	30	23		302	73
Thirty-four Normal Subjects								
Normal range of variation	106-132	5-15	19-31	35-53		21-39	5-15	..

Note: All values except those in the last column are given as mg. hexose per 100 ml.

* Figures in these columns represent cases in which the mobilities of the "abnormal" fractions were such that it was found suitable to change the standard system used when cutting the paper strips before elution of the color to avoid dividing the abnormal component between two of the standard fractions.

same percentages in all serum polysaccharides. In order to investigate the correctness of this assumption the relative contents of the protein-bound sugars were calculated. (Table IV.) For comparison, the value for the protein-bound hexoses was arbitrarily taken as 2. The table shows that the proportions between the sugars

are, on the average, 2 (hexose), 1.5 (hexosamine) and 0.8 (sialic acid). In many serums of both groups the interrelationship varies among the sugars more than can be ascribed to chance. This implies that the polysaccharide content of the different glycoproteins is of varying com-

TABLE VI
MOBILITY, ULTRACENTRIFUGAL SEDIMENTATION VELOCITY,
CONCENTRATION AND COMPOSITION OF THE "ABNORMAL"
COMPONENTS

Case	Mobility	Sedimentation Constant (S ₂₀)	Concentration in Serum (g per 100 ml.)	Hexose Content (%)	Polysaccharide Content (%)
<i>Group I. Patients with Myeloma</i>					
1, A. O.	γ_2	7	7.5	0.9	1.6
2, K. J.	γ_2	...	3.3	0.8	1.7
3, H. H.	$\gamma_2\text{-}\gamma_3$...	6.0	1.5	3.7
4, H. F.	γ_2	...	6.5	0.9	2.0
5, A. N.	γ_2	...	4.6	0.8	1.8
6, A. J.	γ_2	...	7.7	1.0	2.1
7, A. L.	γ_2	...	2.7	1.2	2.9
8, O. K.	$\gamma_1\text{-}\gamma_2$...	7.2	0.9	1.8
9, K. L.	$\gamma_1\text{-}\gamma_2$...	5.6	0.9	2.2
10, A. S.	γ_1	...	0.8	0.5	1.4
11, J. B.	$\beta_2\text{Ca-}\gamma_1$	10	5.3	3.3	6.6
12, W. J.	$\beta_2\text{-}\gamma_1$...	2.0	0.7	1.6
13, O. H.	$\beta_2\text{-}\gamma_1$	10	4.7	3.5	7.0
14, G. L.	$\beta_2\text{-}\gamma_1$	<7	5.0	1.3	...
15, J. C.	$\beta_2\text{Ca}$	10	3.6	3.0	6.3
16, S. N.	$\beta_2\text{Ca}$...	5.0	3.8	8.3
17, N. J.	$\beta_2\text{Ca}$	10-11	2.5	4.2	7.2
18, A. H.	$\beta_1\text{-}\beta_2\text{Ca}$...	6.4	3.5	6.3
<i>Group II. Patients with Other Diseases</i>					
19, N. W.	γ_2	19	1.9	6.4	13
20, M. F.	γ_2	19	5.0	3.5	7.0
21, S. W.	γ_2	19	2.6	5	10.6
22, F. F.	γ_2	19	4.1	4.9	8.7
23, M. O.	γ_2	19	5.4	6.0	10.1
24, N. R.	γ_2	19	4.0	5.1	8.9
25, G. M.	γ_2	...	5.5	5.0	8.5
26, G. A.	γ_2	19	0.5	7.4	14.7
27, E. S.	$\gamma_1\text{-}\gamma_2$	19	2.6	9.4	15.8
28, E. P.	$\gamma_1\text{-}\gamma_2$	<9	0.9	4.4	9.5
29, H. K.	γ_1	...	0.5	8.6	16.8
30, M. B.	$\beta_2\text{Ca-}\gamma_1$	19	5.2	5.1	8.8

position. This variation is, however, not so large as to invalidate the principles adopted for calculating the carbohydrate content of the different electrophoretic components, because these are only to be used for rough comparative studies. Investigations are in progress to elucidate the value of the method by studying polysaccharides from isolated "abnormal" glycoproteins.

Before the strip stained for polysaccharide was cut into segments, the strips stained for protein and polysaccharide were compared visually to decide whether the pathologic protein compo-

nent appeared as a distinct band of one and the same mobility in both strips. Such agreement was obtained for all of the cases described herein. This inspection alone is enough to obtain a rough idea of the relative carbohydrate content of the abnormal component.

The calculations made on the basis of the distribution of periodic acid-Schiff reacting substances after electrophoresis and on the basis of anthrone-reacting substances in whole serum are given in Table v, at the bottom of which the normal distribution is also indicated. The percentage of the color recovered from the same paper segment containing the abnormal protein component was multiplied by the value found for the total serum polysaccharide, whereby a value was obtained for the polysaccharide content of the paper segment which contained not only the normal components but also the pathologic fraction. This value was then corrected, as an approximation, for the amount of carbohydrate ascribable to the normal glycoproteins within this paper segment.

The corrected absolute hexose value for the abnormal fraction was then used to calculate the hexose content of the abnormal component and to obtain a corrected percentage of the periodic acid-Schiff color of the abnormal component. (Table v, last column.) This value was multiplied by the value found for total serum polysaccharide to obtain a value for the serum polysaccharide referable to the abnormal component.

Table vi gives various data on the abnormal components. A semi-quantitative estimation of the fractional contents of polysaccharide and hexose in the abnormal fraction was obtained from the ratios between the absolute values of the polysaccharide and hexose contents, and the protein content, as given in Tables iii and ii. The ratio is given as per cent. No allowance was made, however, for the fucose values.

The hexose and polysaccharide contents and the electrophoretic mobilities of the various abnormal components are compared in Figures 3 and 4, from which it is apparent that in patients in group i (myeloma) the carbohydrate content was low when the mobility was low but showed a tendency to increase with higher mobility. Serums from patients belonging to group ii regularly contained components with a higher percentage of carbohydrate than components from myeloma serums, if the mobility was taken into account. There was no overlapping between the two groups in this material.

CLINICAL OBSERVATIONS

In group I, which consisted of the myeloma cases (1 to 18), the clinical picture was typical and the diagnosis as a rule was founded on analysis of sternal bone marrow biopsy speci-

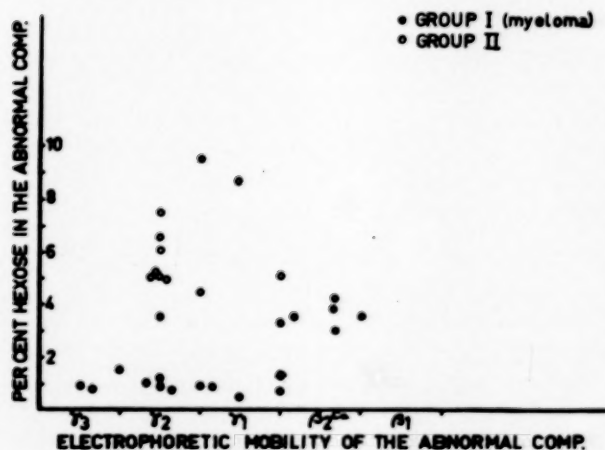


FIG. 3. Correlation between hexose content of the "abnormal" component and electrophoretic mobility.

mens, roentgenographic signs of osseous changes, anemia and sometimes also on the presence of Bence Jones protein in the urine. As a rule, post-mortem examinations were also carried out. Being so clearcut, these cases hardly call for comment.

Group II, however, was of particular interest since it contained so many cases which could not be grouped into well established diagnostic entities. Our interest was focused mainly on the patients (Cases 20 to 24 and 30) with a condition that may be regarded as macroglobulinemia. Typical macroglobulinemia is most common among males above fifty. This disorder is characterized by normochromic anemia, a tendency to increased number of lymphocytes in the blood and generalized enlargement of lymph nodes, gingival and nasal bleeding usually without purpura but sometimes with intraocular hemorrhages, no focal osseous changes and no bone pain. Sternal puncture shows the presence of numerous lymphocytic elements probably belonging to the reticulum cell series. The cytoplasm of these cells often shows budding and signs of shedding. Spindle-shaped cells are common. The erythrocyte sedimentation rate usually is above 80 mm./hour because of the presence of an abnormal globulin component in high concentration. In later stages the serum albumin is markedly decreased and this probably

explains the pronounced edema in the final stages. Electrophoresis shows one pathologic component that migrates with the β or γ fraction or intermediate between these two. This protein has a high sedimentation constant (17 to 20 S) indicating a molecular weight of

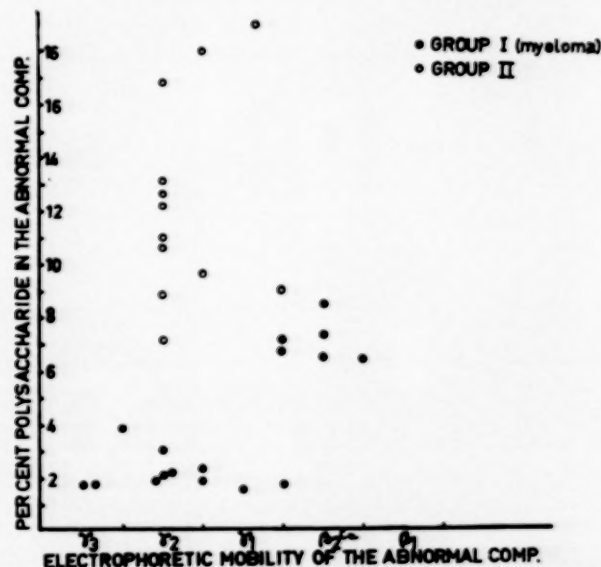


FIG. 4. Correlation between polysaccharide content of the "abnormal" component and electrophoretic mobility.

about 1 million. The solubility of these macroglobulins varies considerably with the temperature. In some cases they precipitate on cooling and thus behave like cryoglobulins. The increase in viscosity of the serum with decreasing temperature is also more marked than in other types of hypergammaglobulinemia. The viscosity temperature index of Waldenström³²

$$\left(\frac{\text{relative viscosity } 13^{\circ}\text{C.} \times 100}{\text{relative viscosity } 37^{\circ}\text{C.}} \right)$$

is usually above 120. The simplest way to screen serums for their macroglobulin content is by the euglobulin test of Sia. However occasional instances of proved macroglobulinemia have been negative to this test. It can regularly be shown that the abnormal electrophoretic component is of the same magnitude as the high molecular component found on ultracentrifugation.

It has already been pointed out that some patients with a high content of macroglobulin in the blood present a clinical picture which differs from what we have described as macroglobulinemia. The grouping of these cases is still uncertain and more experience is needed before it can be attempted.

Only personally studied cases (19, 23 and 24) will be described. The history of a patient (Case 21) seen in consultation by one of us (J. W.), was quite characteristic of macroglobulinemia. Judging from clinical data placed at our disposal by Dr. R. Creyssel (Cases 20, 22), Professor F. Koller (Case 21) and Professor P. Cazal (Case 30) the clinical picture in their patients was also indicative of macroglobulinemia.

CASE REPORTS

CASE 19. This man, N. W., was born in 1874. The personal history revealed nothing of interest. In August, 1955, the erythrocyte sedimentation rate was 92 mm./hour. He complained of pain in the shoulders. The liver was found to be enlarged at that time. On admission in December, 1955, the patient was tired and slightly cyanotic. No hemorrhages were observed. The liver was considerably enlarged. The spleen was not palpable. The mobility of both shoulder joints was limited. Roentgenography of the chest showed a shadow in the right lower lobe and destruction of the fourth and fifth ribs corresponding to this shadow. A sclerotic round focus was also observed in the second lumbar vertebra. Otherwise there were no signs of skeletal metastases or tumors. The patient received roentgen treatment of his pulmonary tumor. His fever increased and anemia developed. There was no albuminuria. Sternal puncture showed nothing remarkable.

The patient died on March 2, 1956. Postmortem examination showed two cerebral metastatic growths. The heart was enlarged (weight, 410 gm.). From one of the ribs a tumor the size of a tennis ball bulged into the lung without infiltrating the parenchyma. The liver was enlarged and contained a large white tumor and several small secondary tumors. A metastatic growth was also found in the left adrenal gland. The tumors showed the histologic picture of malignant cholangioma. In the metastases the picture resembled an adenocarcinoma.

CASE II. This woman, M. O., was born in 1918. She had had nasal and diffuse gingival bleeding for twelve years. In August, 1953, the erythrocyte sedimentation rate was found to be extremely high. Repeated examination failed to reveal signs of myeloma but in November, 1954, Bence Jones protein was reported to be present in the urine. Sternal puncture showed no plasma cells or pathologic lymphocytes. Roentgenographic examination revealed no bone changes and bone pains were denied. The patient also had brief episodes of retinal hemorrhage on the right side. She had persistent normochromic anemia (about 2.5 million red cells) and the erythrocyte sedimentation rate was about 150 mm./hour. The white blood cell and platelet counts were normal. The bleeding time and the coagulation time were increased. The blood contained large amounts of an

abnormal gamma globulin with a sedimentation constant of 18 S, Sia's test was positive. The clinical picture of mucosal and retinal bleedings is typical of macroglobulinemia but no signs of lymphadenopathy or lymphocytosis were observed. The presence of Bence Jones protein in the urine must be noted. Tentative diagnosis: atypical macroglobulinemia.

CASE 24. This man, N. R., was born in 1886. The previous history revealed nothing of interest. In 1944 he had had hematuria of uncertain cause; in 1945 gallstones and gastric ulcer; in 1948 a recurrence of hematuria. A urethral stricture was found. The erythrocyte sedimentation rate was 19 mm./hour on admission. In August, 1954, the patient complained of anesthesia of the heels and somewhat later of severe pain in the fingers and toes. This was followed by increased loss of sensation of both hands and feet. The erythrocyte sedimentation rate was now 120 mm./hour. The patient was readmitted in March, 1955. The liver and spleen were not palpable. No retinal bleedings, pareses or reflex disorders were observed. Sensation in the hands and feet was definitely impaired. Lumbar puncture showed no signs of a pathologic condition. Histamine and neutral red test revealed refractory achlorhydria. A normochromic anemia (3.2 million red cells) was present. The white blood cell count was normal. The body temperature was normal. The urine contained traces of protein. Marked hyperglobulinemia was present. Roentgenographic examination showed no signs of myeloma. Sternal puncture revealed nothing of special interest.

Treatment with vitamin B₁₂ in large doses produced no demonstrable improvement. On a later occasion the blood pressure was found to be fairly low (105/50 mm. Hg). Electrocardiographic studies showed nothing of interest. The pain in the fingers and feet was severe. Proteinuria was regularly demonstrated but no Bence Jones protein was found. There were no signs of hemorrhagic diathesis except the episodes of hematuria previously noted.

The patient died on June 6, 1956. The postmortem examination showed signs of lymphatic leukemia with marked enlargement of para-aortal lymph glands and an infiltration the size of an orange in the liver. The microscopic picture was typical. A small spinocellular pulmonary carcinoma was also found.

In this case the picture was dominated by findings of the type seen in polyneuritis. Such cases, with the other signs of macroglobulinemia, have earlier been published. There were no clinical signs of lymphatic leukemia. Diagnosis: macroglobulinemia.

In Cases 25 and 27 the diagnosis was uncertain but the records and the clinical findings might possibly suggest some kind of collagen disorder in spite of the fact that dysproteinemia in collagen diseases is characterized by broad bands and not by narrow peaks, as found in these cases.

CASE 25. This woman, G. M., was born in 1882. She was seen in consultation with Dr. H. Silwer, who gave us his notes on the previous history. In 1951 the patient noticed large erythematous patches on both cheeks. These symptoms appeared after exposure to bright sunshine. About the same time dyspnea and chest pain radiating to the left arm developed. She had slight hypertension. The erythrocyte sedimentation rate was 70 mm./hour. The bone marrow appeared normal. Electrophoretic examination of the serum showed 3 per cent gammaglobulin with an albumin value of 2.2 per cent. The erythrocyte sedimentation rate remained very high and Bence Jones proteinuria was found. It was also noted that the serum became gelatinous on cooling. The patient was admitted to the Medical Clinic, Malmö General Hospital in January, 1955. The blood pressure was 190/105 mm. Hg. Laboratory studies showed a normochromic anemia of 3 million erythrocytes, a relative lymphocytosis (50 to 60 per cent) and a few plasma cells. There was no proteinuria. Roentgenographic examination revealed no signs of myeloma. No L.E. cells could be found. The serum contained large amounts of cryoglobulin and gave a strongly positive euglobulin test (Sia). No definite diagnosis could be made but myeloma and lymphatic leukemia were regarded as very improbable. The patient was reexamined in February, 1956, without further clarification of the diagnosis.

CASE 27. This woman, E. S., was born in 1871. The diagnosis was never definitely established. Her previous history contained nothing of interest. In 1936 a carcinoma of the uterus was treated with radium with excellent results. In 1947 the patient had cystopyelitis. The erythrocyte sedimentation rate was then 76 to 88 mm./hour. In 1947 she complained of a painful swelling of the metacarpophalangeal joints. Later back pain developed also for which she was admitted to the medical department in 1948. At that time there were no signs of active arthritis. Myeloma was suspected because of slight anemia and an erythrocyte sedimentation rate of about 100 mm./hour with subsequent values, determined on various occasions regularly increased. The patient still had pain in the back and in one or two of the finger joints. Sometimes the pain in the fingers was extremely severe but soon abated. Her general condition was excellent and she had an unusually keen interest in life for her age. The serum uric acid was not increased. Roentgenographic examination of the hands showed no signs of chronic arthritis. Later an erythematous patch tender to palpation appeared over the left inner malleolus which, however, disappeared spontaneously after two days. Although the patient still has joint pain her condition has improved since the previous examination. At the last examination in October, 1956, there were definite signs of arthritis in two fingers with marked swelling. Status as before.

In this case myeloma could be excluded since the erythrocyte sedimentation rate had been increased for the previous ten years, during which time her general condition improved. Roentgenographic examination of the skeleton showed no signs of myeloma and the urine contained no Bence Jones protein, nor has anemia developed. The patient would not permit sternal marrow puncture. It is noteworthy that she had suffered from carcinoma, since Wuhrmann³³ has repeatedly stressed the association of macroglobulinemia with malignant tumors. (cf. also Case 19.)

Two instances of leukemia, Cases 26 and 29, belong to group II. The serum from one of these patients (Case 29, chronic lymphatic leukemia) together with an abstract of the history was sent to us by Dr. med. Helmuth Krause.

The other (Case 26) was an instance of atypical myeloid leukemia. The patient, a woman, was born in 1886. Since December, 1952, she had felt tired, and had lost 7 Kg. She was admitted in July, 1953. There were no palpable lymph nodes. The spleen and liver were markedly enlarged. On admission: white blood cell count 358,000 per cu. mm., mostly "lymphocytes," hemoglobin 45 per cent, erythrocytes 2.4 million, platelets 148,000 per cu. mm. The total serum protein was 3.6 gm. per cent with gamma globulin 0.83 gm. per cent. Remarkably, however, the gamma fraction showed a very narrow band resembling that seen in myeloma. When the serum was cooled (+4°C.) in a conical centrifugal tube a small gel appeared after twenty-four hours in the bottom of the tube. The water test was negative. The patient's serum also gave positive Wassermann, Meinicke and Kahn reactions and a positive Middlebrook-Dubos test. She received blood transfusions, vitamins, iron and arsenic, and the blood picture improved considerably. Later the patient was treated with myleran, with excellent effect. Her general condition remained good until January, 1956, when she suffered a severe relapse and died on April 8. Postmortem examination revealed myeloblastic leukemia. The case will be published in detail by S. E. Björkman.

CASE 28. This patient, E. P., was a healthy blood donor. During an observation time of more than two years no physical or laboratory findings indicating any disease except the abnormal γ component has been found. The water dilution test was negative. Ultracentrifugal investigation revealed no heavy component in abnormal concentration. This case will be investigated further by Dr. B. Nosslin.

COMMENTS

All of the serums analysed contained one component in the β or γ region in abnormal concentration which, after paper electrophoretic separation, appeared as a distinct band. The concentration of this component in the serum

varied widely from case to case, with 7.7 gm. per cent as a maximum and 0.5 gm. per cent as a minimum value. The serum protein pattern in some cases also differed from normal in other respects: (1) a pronounced decrease in serum albumin and (2) a moderate increase of the α -fractions, which has been observed in renal injury as well as in malignant and infectious processes.

The normal serum content of protein bound hexoses is relatively constant ($M = 119$, S.D. ± 9); about 80 per cent of these glycoproteins are normally found in the α and β fractions. In this pathologic material (Table II), the protein-bound hexoses in the serum, however, showed very wide variations despite the fact that the magnitude of the α -fractions varied only slightly. (Table I.) It was therefore usually easy to decide whether the abnormal serum protein fraction was relatively rich or poor in carbohydrates. If the paper electrophoresis showed an abnormal component and at the same time an increased value for protein-bound hexoses, an approximate estimation of the carbohydrate content of the pathologic fraction could be obtained by dividing the value of the protein-bound hexoses (minus the normal value) by the value for the protein concentration of the abnormal component. In this simple way reliable information could be obtained, however, only when the concentration of the abnormal component in serum was at least 1 per cent; if the concentration is lower, the carbohydrate content of the α and β -fractions is so large in relation to the serum protein-bound hexoses that the carbohydrate content of the abnormal protein fraction can be estimated only after electrophoretic protein fractionation, with subsequent periodic acid-Schiff staining. Preparative electrophoresis or protein fractionation by other technics may also be employed for this purpose.

Table III gives data on the total content of protein-bound hexoses, hexosamine, sialic acid and fucose in the various serums. These values are, however, of relatively limited interest because different glycoproteins vary widely in carbohydrate content and in their relative values of hexose, hexosamine and sialic acid. Schultze and Biel³⁴ recently showed similar variation in different electrophoretically separated protein fractions of normal serum obtained by preparative electrophoresis, and for various isolated glycoproteins belonging to the α -group. Table IV shows the relative variation of the protein-bound

carbohydrate components in our serums. It can be calculated from the material presented by Schultze and Biel³⁴ that the ratio: protein-bound hexose/hexosamine/sialic acid for normal proteins of the α and β groups vary over the range 2/0.9–1.4/0.9–1.7, and for the γ group 2/0.8–1.2/0.45–0.6. Most of our serums also fall within these limits, but most of the myeloma serums had strikingly high contents of hexosamine. This suggests that the abnormal fraction contains protein-bound hexoses and hexosamine in a variable and often abnormal ratio. The relative sialic acid content of the polysaccharides also varies, but this is seen in normal serum proteins too. No relation was found between the relative composition of the polysaccharides and the electrophoretic mobility of the pathologic fractions. The heterogeneity of the group of pathologic fractions examined is apparent from the varying electrophoretic mobility as well as from the varying polysaccharide content and composition. Only the abnormal component of serums from patients with macroglobulinemia showed a relatively uniform picture. Of the seven patients examined all except one showed the same electrophoretic mobility as the bulk of the normal γ -globulins. It might also be mentioned that these serums containing macroglobulins gave a distinctly positive reaction with Sia's water dilution test, except the serum with electrophoretic β mobility. In all other serums, independently of the diagnosis, the water dilution test was negative. This agrees with previous (unpublished) findings of Pedersen and Waldenström that in cases of macroglobulinemia with an abnormal component with γ_2 mobility, a positive euglobulin reaction is regularly given. Waldenström has observed three macroglobulinemic serums with β mobility in which the euglobulin reaction was negative. Judging from similar observations published in the literature, this relationship between electrophoretic mobility and euglobulin reaction could well be a regular phenomenon in macroglobulinemia.

Approximate values for the polysaccharide content are given in Table V. Comparison of the polysaccharide content of abnormal components will not give a correlation corresponding directly to the clinical diagnosis. Only cases of macroglobulinemia regularly showed the same relatively high carbohydrate content. This corresponds with the few observations previously cited. In the myeloma group the carbohydrate

content varied widely, an observation also compatible with the findings of earlier workers in this field. On the other hand, when the results are reproduced graphically with the aid of a coordinate system in which the abscissa represents the electrophoretic mobility of the abnormal component and the ordinate its carbohydrate content (Figs. 3 and 4), the serums in the myeloma group were found to differ from the others. In the myeloma group (I) the carbohydrate content was found to be low in the components with γ_3 and γ_2 mobility, and varied from low to relatively high in the components with γ_1 and β_1 mobility. In group II no such relationship was found between the polysaccharide content and the electrophoretic mobility. It is interesting, both from a theoretic and a practical point of view, to note that the graph shows no overlapping (Figs. 3 and 4) between the myeloma group (I) and the other conditions studied (group II). It is also evident from a comparison of Figures 3 and 4 that the same difference between group I and II obtains whether the polysaccharide or the hexose contents of the abnormal components are used for classification. This suggests that, from a clinical point of view, the estimation of hexose gives information of the same value as estimation of all the simple carbohydrates. The number of serums so far investigated is as yet not large enough to permit valid conclusions as to the differential diagnostic value of this observation but analysis of the literature on carbohydrate determinations in isolated abnormal components and of the polysaccharide pattern suggests that this phenomenon may be of regular occurrence. In most of these publications, however, the carbohydrate content is not stated and can only be estimated from the diagrams given of the protein and carbohydrate distribution of electrophoretically separated serums.

SUMMARY

The serum protein and polysaccharide distribution in thirty serums from patients with certain diseases such as myeloma were analysed. The material included eighteen myeloma serums (group I) and twelve serums (group II) from six patients with macroglobulinemia, two with lymphatic leukemia and four with allied conditions.

The polysaccharide content of the "abnormal" protein components showed considerable variation in both groups. However the relation-

ship found between the electrophoretic mobility and polysaccharide content of the "abnormal" serum components of the two groups suggested a difference in the chemical composition of the abnormal components of the serums, a difference of possible diagnostic value.

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Pulmonary Disease Following Chronic Chemical Ganglionic Blockade*

A Clinical and Pathologic Study

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CHRONIC chemical blockade of autonomic ganglia in combination with administration of hydralazine usually controls the malignant stages of hypertension in human beings.¹ Sometimes, however, therapy is complicated by the development of pulmonary disease^{2,3} manifested clinically by extreme tachypnea in patients without cardiac failure and with plasma non-protein nitrogen levels less than 60 mg. per cent. Anatomically the lesions resemble those of so-called "uremic pneumonia."⁴ It appears that methonium salts can occasionally act like nitrogen retention as a factor in the pathogenesis of this pulmonary disease. Since the presence of fibrin in the alveoli was, in our experience, the most constant anatomic feature of this disease, we have termed the pathologic process "fibrinous pneumonitis."

To define the process more precisely and to evaluate the possible etiologic role of therapy, anatomic changes in the lungs were studied in methonium-treated patients with a primary anatomic diagnosis of arteriolar nephrosclerosis and, to provide control observations, in comparable untreated patients. To exclude intermittent left heart failure as a cause of the fibrinous pneumonitis that followed methonium therapy, the lungs of patients with mitral stenosis were also examined. Since all methonium-treated patients with pulmonary lesions had had malignant stages of hypertension and since all but one had nitrogen retention before treatment, clinical comparisons were limited to azotemic patients with similarly severe hypertension. Finally, the courses in patients whose hypertension was successfully controlled by

therapeutic regimens were compared with the courses in patients in whom the therapeutic regimen had not been successful.

METHODS

Material. Two groups of autopsied patients were selected for thorough study from the files of the Department of Pathology, Washington University. The sixty-seven members of the first group comprised all patients with the primary anatomic diagnosis of arteriolar nephrosclerosis who died between September 1, 1943 and September 1, 1951. Since none of these patients ever received any methonium compound they are hereinafter referred to as "untreated patients." Their average age was fifty with a range from twenty to eighty years; twelve were Negro and twenty-one were women. The twenty-seven members of the second group comprised all patients with the same primary anatomic diagnosis dying between September 1, 1951 and September 1, 1955 after receiving at least 30 gm. of oral methonium salts during their last month of life. They are therefore hereinafter referred to as "methonium-treated patients." Their average age was forty-seven with a range from twenty-seven to sixty-five years; thirteen were Negro and nine were women.

In addition, the postmortem cardiac and pulmonary changes of thirty-nine adult patients with an anatomic diagnosis of "moderate" or "advanced" mitral stenosis were examined. Finally, the pretreatment blood pressure and azotemia, the length of therapy and the methonium dosage were tabulated for twenty-eight living patients who had had hemorrhagic and exudative retinitis with papilledema, nitrogen retention and mean diastolic pressures exceeding 120 mm. Hg before therapy.

Pathologic Methods. From each patient's autopsy protocol the gross description of the lungs and the weight of lungs, heart and kidneys were obtained.

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Sections of lung stained with hematoxylin and eosin were examined, and selected cases were further studied after staining with the periodic acid-Schiff technic, Weigert's fibrin stain, aldehyde fuchsin-van Gieson-hematoxylin, and with phosphotungstic acid-hematoxylin. All sections were examined particularly for "hyaline" membranes lining the air spaces, deeply eosinophilic granular or fibrillar (fibrin-like) material in the alveoli and organization of intra-alveolar exudate. In addition, a special search was made for necrosis of alveolar walls, fibrin thrombi in capillaries, edema, intra-alveolar hemorrhage, hemosiderin-filled macrophages, capillary distention, fibrous thickening of alveolar walls and cuboidal cells lining alveoli. The pathologic changes were graded *slight* if less than 10 per cent of the tissue available for microscopic study was estimated to be involved, *moderate* if 10 to 25 per cent was involved and *advanced* if over 25 per cent was involved.

Clinical Methods. Clinical considerations were limited to those autopsied patients who had had malignant hypertension* as manifested by (1) a mean supine diastolic pressure greater than 120 mm. Hg at hospital rest, (2) hemorrhagic and exudative retinitis with papilledema, and (3) severe renal disease manifested by constant albuminuria and less than 10 per cent excretion of intravenously injected phenol red within fifteen minutes. The patients included in the clinical discussion all had pretreatment azotemia which was considered to be of renal origin on the basis of its persistence after the evidence for cardiac failure had disappeared. Forty untreated and nineteen methonium-treated patients fulfilled these criteria. The average age of the former was forty-five with a range from twenty to sixty-three years; ten were Negro and thirteen were women. The average age of the latter was forty-six with a range from twenty-seven to sixty-five years; twelve were Negro and eight were women. Their antihypertensive regimen always included ganglionic blocking agents in dosages depending on the systolic pressure of the seated patient, and a simultaneously administered fixed dose of hydralazine as previously described.⁵ Except in emergencies all medication was oral. Untreated patients received neither these drugs nor alkaloids of *rauwolfia* or *veratrum*.

The mean control diastolic pressure was obtained for each methonium-treated patient at rest in the hospital before any therapy; except for two patients with hypertensive encephalopathy and three with heart failure, each mean value was the average of eight to thirty-seven sphygmomanometric readings taken at four-hour intervals with the patient in the

supine position. Temperature, pulse, respiration and blood pressure were recorded six times a day throughout the hospital course. Except for the three patients with heart failure the degree of azotemia was determined before any medication and without evident cardiac decompensation; thereafter it was followed closely. In our laboratory the upper limit for normal circulating non-protein nitrogen in the plasma after deproteinization by zinc hydroxide⁶ is 25 mg. per 100 ml., the low value being due to precipitation of glutathione, ergothioneine, uric acid and perhaps other substances that are not removed by the more commonly employed phosphotungstic acid procedure. Frequent plasma sodium and carbon dioxide determinations were made, as were white blood cell counts. In addition, various procedures to evaluate cardiac and pulmonary function were performed, including arm-to-tongue circulation time measured by decholin[®] injection, venous pressure, vital capacity, oxygen saturation and pH of arterial blood. Untreated patients were followed less closely; however, all available comparable clinical data were assembled. In the period prior to frequent sodium determinations, chloride concentrations in the plasma were tabulated.

Each methonium-treated patient who returned home was given a sphygmomanometer and adequate instruction for its use. The levels of blood pressure and the intake of drug after discharge from the hospital were obtained by averaging the recordings made five times a day by each patient for a period of one week. The mean variation in systolic pressure of the seated patient is a measure of vasomotor instability;⁷ it was calculated by averaging the difference between each of thirty-five readings and their mean during the time of the poorest control of blood pressure at home. The average intake of methonium compounds and the length of therapy were tabulated; the maximum daily dose ingested was based on a period of at least seventy-two hours. The maximum dose of hydralazine was similarly ascertained.

RESULTS

Pathologic Data. Results of the comparative pathologic study are presented in Table 1. The average ages of the patients in each group were approximately the same. The average weights of the hearts were 549 gm. for methonium-treated patients, 618 gm. for untreated patients and 532 gm. for patients with mitral stenosis. The average weights of the lungs were 1,410, 1,283 and 1,352 gm., respectively, for the three groups. The average weights of the kidneys were 299 gm. for methonium-treated patients and 266 gm. for untreated patients; arteriolar necrosis was diagnosed microscopically in 41 per cent of the former and 45 per cent of the latter. There was no correlation between the presence of arteriolar necrosis and of fibrinous pneumonitis in hyper-

* The term "malignant hypertension" as used hereinafter is a clinical diagnosis; nitrogen retention may or may not be present. It should not be confused with the anatomic term: malignant nephrosclerosis, which is characterized by necrotizing arteriolar lesions and is accompanied by azotemia.

TABLE I
PATHOLOGIC DATA

	Untreated	Methonium-Treated	Mitral Stenosis
Number of cases	67	27	39
Age of patients (average)	50 yr.	47 yr.	55 yr.
Heart weight (average)	618 gm.	549 gm.	532 gm.
Lung weight (average)	1,283 gm.	1,410 gm.	1,352 gm.
Kidney weight (average)	266 gm.	299 gm.
Arteriolar necrosis (incidence)	45%	41%
Fibrinous pneumonitis (incidence)			
Slight	9%	11%	15%
Moderate	15%	26%	3%
Advanced	10%	22%	0%
Total	34%	59%	18%
Hyaline membrane (incidence)	16%	41%	6%
Intra-alveolar fibrin masses (incidence)	34%	59%	18%
Organized exudate (incidence)	18%	52%	6%

tensive patients. The 59 per cent incidence of fibrinous pneumonitis in methonium-treated patients is significantly greater ($p < 0.05$) than the 36 per cent incidence in untreated patients. Morphologically indistinguishable pulmonary disease was present in 18 per cent of the patients with mitral stenosis: in only one instance, however, was it classified as moderate and in none as severe. When the extent and severity of "hyaline membranes," intra-alveolar fibrin and organization of exudate were tabulated, qualitative differences were not apparent between the overall process in methonium-treated and untreated patients. Organization of the fibrinous exudate was more common in the former, probably indicating a longer survival. Both groups together included nineteen patients, with more than 100 mg. non-protein nitrogen per 100 ml. plasma, who had fibrinous pericarditis but the association between it and fibrinous pneumonitis was no greater than would occur by chance alone.

The gross description of the lungs at autopsy almost invariably read "congestion and edema." As the microscopic study progressed it became apparent that a pulmonary pathologic process of rather constant character was present in both methonium-treated patients and untreated subjects. The histologic findings were consistent with the condition designated by others as "uremic pneumonia,"⁴ "fibrinous edema"³ or, if accompanied by extensive intra-alveolar organization of fibrous tissue, "carnification of the

lung."³ The term fibrinous pneumonitis is used here to designate this pulmonary disease, which is always characterized by fibrin masses in the air spaces of the lungs and is frequently associated with a hyaline-like membrane lining the walls of the alveolar ducts and atria. A notable feature of the condition is the tendency of the intra-alveolar fibrin to become organized by the ingrowth of fibrous tissue. (Fig. 1.) There was considerable variation from case to case in the amount and the degree of organization of the fibrin masses. The deposits of intra-alveolar fibrin varied from loose, lacy strands lying within densely eosinophilic edema fluid to heavy compact "balls" of fibrin filling and distending alveolar sacs. The fibrin was well demonstrated by the phosphotungstic acid-hematoxylin stain and the Weigert fibrin stain. (Fig. 2.) Hyaline-like membranes consistently failed to stain with phosphotungstic acid-hematoxylin (Fig. 3) but were faintly stained with the Weigert fibrin stain and the periodic acid-Schiff technic. Occasionally, hyaline-like membranes were associated with collapse of the alveoli and distention of the atria and alveolar ducts (Fig. 4) similar to that seen in hyaline-like membrane disease of newborn infants.⁸ Collapse of alveoli often gave the impression of thickened alveolar walls but no widespread increase of fibrous tissue within alveolar septae was demonstrable. In areas containing organized intra-alveolar exudate the alveolar walls were sometimes irregularly thickened by fibrous tissue, apparently the result of



FIG. 1. Methonium-treated patient without uremia (ninth patient of Tables II and III). Fibrous tissue in air spaces, the result of organization of intra-alveolar fibrin. The alveolar walls are not affected; hematoxylin and eosin, original magnification $\times 660$.

organization of exudate adherent to the alveolar walls. Although an increase in alveolar macrophages was common, neutrophils were seldom seen in areas of fibrinous pneumonitis even when foci of bronchopneumonia were present in other areas. Cuboidal alveolar lining cells were occasionally present but could not be related to the presence of intra-alveolar fibrin or to the hyaline-like membrane. Pulmonary capillary engorgement and intra-alveolar hemorrhage were frequent and often especially prominent in and about areas containing intra-alveolar fibrin and hyaline-like membranes. Fibrin thrombi were not encountered in the pulmonary capillaries and no other associated vascular disease was present. Acute bronchopneumonia was found in approximately one-third of both methonium-treated and untreated patients. No relationship



FIG. 2. Methonium-treated patient without uremia (eighth patient of Tables II and III). Masses of fibrin fill alveoli; Weigert's fibrin stain, original magnification $\times 390$.

between this infection and fibrinous pneumonitis was apparent. Necrosis of alveolar walls was occasionally present in areas of bronchopneumonia but was not seen except in association with these foci of bacterial inflammation.

Clinical Data. Figure 5 indicates the relationship between the level of non-protein nitrogen in the plasma and postmortem pulmonary findings in the nineteen methonium-treated and the forty untreated patients with malignant hypertension and pretreatment renal azotemia. Only one of the untreated patients died with less than 60 mg. non-protein nitrogen per 100 ml. plasma while eight of the methonium-treated patients died. All eight had a similar terminal clinical course and fibrinous pneumonitis.

In Table II the terminal episode has been described in terms of nitrogen retention, vital signs, circulation time, leukocytosis and circulating



FIG. 3. Methonium-treated patient with uremia. A dense hyaline-like membrane lines the walls of an atrium and alveolus; periodic acid-Schiff, original magnification $\times 390$.

electrolyte concentration for each of the methonium-treated patients who had fibrinous pneumonitis.* Average values for this group of patients were compared with corresponding data for the methonium-treated patients who did not exhibit fibrinous pneumonitis and for those who had uremia. A similar comparison was made for untreated subjects, both with and without fibrinous pneumonitis. Tachypnea and to a lesser extent tachycardia were the most obvious clinical abnormalities associated with non-uremic fibrinous pneumonitis following administration of methonium. The dyspnea, unlike that of left ventricular failure, was usually improved by placing the patient in a supine position. Moreover, the circulation time was

* The ninth patient in the table is the only one in whom fibrinous pneumonitis developed without ever having nitrogen retention. For this reason he was not included in the figures cited in the text.

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FIG. 4. Case 1. Methonium-treated patient without uremia. The markedly dilated air spaces are alveolar ducts and atria. Alveoli are distorted and partially collapsed. In areas of complete collapse of alveoli the apposition of alveolar walls can easily be mistaken for an increase in thickness of a single alveolar wall; hematoxylin and eosin, original magnification $\times 66$.

relatively normal. The venous pressure was 200, 165, 175, 108 and 120 mm. saline in the second, fifth, sixth, eighth and ninth patients of Table II, respectively. The observed vital capacity was below 1.0 L., the minute volume of respired air was 19 and 23 L. in the fifth and eighth patients, respectively; the oxygen saturation of arterial blood was 95 and 97 per cent of capacity and its pH was 7.3 and 7.4, respectively. For the sixth, eighth and ninth patients the pH was 7.4, 7.5 and 7.5, respectively. The carbon dioxide content of plasma was only slightly reduced, with no obvious differences among the various groups. The urine was uniformly acid with a pH consistently below 5 in all patients. The hyponatremia which has been reported to be associated with "uremic pneumonia"⁴ was not striking although the patients with fibrinous

pneumonitis did have slightly lower plasma sodium or chloride levels. Elevation of body temperature was common in all groups but was not well correlated with fibrinous pneumonitis. Circulating leukocytes were increased but counts were made in less than half of the untreated

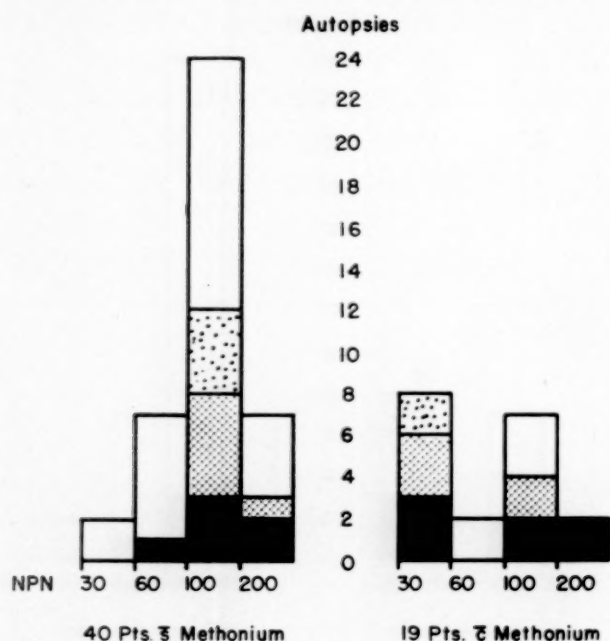


FIG. 5. Fibrinous pneumonitis in patients with malignant hypertension as a function of maximum nitrogen retention more than forty-eight hours before death. The open bars indicate patients without fibrinous pneumonitis, the darkened bars patients with the typical anatomic changes. Stippling represents mild changes, cross hatching represents moderate changes, solid areas represent severe changes.

patients with or without fibrinous pneumonitis and are difficult to evaluate because of associated infection. The lungs were usually clear to percussion and auscultation. The roentgenologic change was a diffuse non-specific infiltration that was disproportionately great for the physical findings. Mental confusion was present in the first, sixth and seventh patients. Of the eight patients in whom fibrinous pneumonitis without uremia developed, in six it occurred in the first eighteen months during which combined hydralazine and methonium therapy was used, and in only one did it develop during the last eighteen months.

In Table III some possible correlations between pulmonary changes and the entire clinical course are tabulated. In the methonium-treated patients in whom fibrinous pneumonitis developed, symptoms referable to hypertension began an average of twelve months before the first entry

to Barnes Hospital, with a range from one to seventy-two months. In the patients who were successfully maintained on therapy, symptoms had been present before treatment for an average of fourteen months with a range from one to one-hundred twenty months. The almost identical mean control levels of diastolic pressure and azotemia in the two groups indicate comparable severity of the original hypertension. Some correlation between mean methonium intake and fibrinous pneumonitis is evident, with higher doses accompanying more severe involvement. Although six of eight methonium-treated patients in whom fibrinous pneumonitis* eventually developed improved sufficiently to be discharged from the hospital on an anti-hypertensive regimen, at home only three achieved an average diastolic pressure as low as 100 mm. Hg despite an excessive total and maximum dose of blocking agent. In contrast, twenty-two of the twenty-eight living azotemic patients maintain diastolic pressures below this level. There was a suggestion that the blood pressure was more labile in those with fibrinous pneumonitis. The greatest mean systolic variation for such patients averaged 20.1 mm. Hg as compared with 14.7 mm. for the living patients.† In no instance did the characteristic dyspnea of fibrinous pneumonitis appear after more than a year of therapy; usually it was present by the sixty-eighth day of treatment. The maximum daily hydralazine intake was high, averaging 0.9 gm. per day with a range of 0.5 to 1.8 gm.; however, none of the autopsied patients had any clinical or pathologic evidence of hydralazine toxicity.

The detailed case report of the only patient in whom fibrinous pneumonitis developed without ever having nitrogen retention (the ninth patient in Tables II and III) has previously been published.² The first patient in Tables II and III is described as Case I in the case report section which follows, with a figure indicating the relationship of blood pressure and other vital signs to therapy. Case II, also described therein, is our only patient suspected of surviving this disease.

COMMENTS

There appear to be no essential qualitative anatomic differences between the pulmonary

* See footnote on p. 41.

† The mean variation,⁷ as an index of the fluctuations occurring under ganglionic blockade, represents the evenness of control attained by the patient. Good control is shown by a mean variation of 9 mm. or less.

TABLE II
CLINICAL FINDINGS TWO TO SIX DAYS BEFORE DEATH IN AUTOPSIED MALIGNANT HYPERTENSIVE PATIENTS
WITH PRETREATMENT AZOTEMIA

Age, Race and Sex	Treated	Fibrinous Pneumonitis	Maximum Non-protein Nitrogen (mg. per cent)	Plasma		Maximum Temperature (°C.)	Maximum Pulse (beat/min.)	Maximum Respiration (breaths/min.)	Maximum Circulation Time (secs.)	Maximum White Blood Count (cells/mm. ³)
				Minimum CO ₂ (mEq./L.)	Minimum Na (mEq./L.)					
Individual Patients										
52, W, ♂	×	×	37	30.5	129	39.0	145	40	..	13,650
47, W, ♂	×	×	44	18.8	113	37.5	110	30*	..	16,450
48, N, ♂	×	×	40	21.6	130	38.0	160	28*	15	5,000
55, W, ♂†	×	×
55, N, ♂	×	×	47	23.6	128	38.6	180	48	13	13,350
52, N, ♀	×	×	36	23.5	135	38.4	125	82	18	22,000
32, W, ♀	×	×	45	19.8	125	38.0	130	32*	12	15,300
49, N, ♂	×	×	60	16.6	127	39.0	190	52	15	24,800
33, N, ♂‡	×	×	25	17.1	137	39.3	135	110	20	13,200
Group Means										
9 patients§	×	×	25-60	21.4	128	38.5	148	54	16	15,460
6 patients	×	×	109-204	23.7	132	38.5	123	30	..	22,100
5 patients	×	0	49-238	23.8	137	37.7	118	27	..	9,300
16 patients	0	×	61-294	23.2	81.9	37.6	106	27	..	24,910
24 patients	0	0	31-295	20.7	88.6	38.2	112	29	..	19,400

* The highest actual value cited on the chart, although marked tachypnea was specially recorded by attending physician.

† Patient died as he re-entered the hospital following a three-day history of lobar pneumonia.

‡ Only patient in the treated group without pretreatment nitrogen retention.²

§ This is the average of the nine individual patients.

|| Chloride levels since sodium determinations were only infrequently done at this time.

disease often associated with uremia and that associated with methonium therapy, although there are individual quantitative variations in the amount of intra-alveolar fibrin, formation of hyaline membranes and organization of the exudate. Because exudation of fibrin is a constant anatomic feature, we have termed the process "fibrinous pneumonitis." The absence of polymorphonuclear leukocytes in the exudate may account for the failure of the exudate to lyse, with resultant organization of the fibrin. Diffuse damage to the pulmonary capillaries is undoubtedly responsible for the exudation of fibrin into alveoli but the mechanism by which this damage is produced remains obscure and there is no morphologic evidence of pulmonary vascular disease. The disease described herein is similar also to so-called "rheumatic pneumonitis." Fibrinous pneumonitis was not encountered

in hypertensive patients whose non-protein nitrogen levels never exceeded 60 mg. per 100 ml. plasma unless they had received methonium salts. This suggests that methonium therapy can replace nitrogen retention as a factor in the pathogenesis of this pulmonary disease.

Drug therapy for patients with malignant hypertension has been accompanied by an increased life expectancy¹ as compared to untreated patients with similarly severe disease.¹⁰⁻¹² Of forty-six patients with malignant hypertension and pretreatment renal azotemia of 30 to 60 mg. non-protein nitrogen per 100 ml. plasma, who have continued to take oral ganglionic blocking agents in combination with hydralazine, twenty-seven are alive after an average of 21.8 months.¹³ Eight of the remainder had a terminal episode characterized by marked

TABLE III

BLOOD PRESSURE AND THERAPY IN MALIGNANT HYPERTENSIVE PATIENTS WITH PRETREATMENT AZOTEMIA

Age, Race and Sex	Living	Fibrinous Pneumonitis	Terminal Uremia	Pre-treatment Diastolic Pressure (mm. Hg)	Pre-treatment Plasma Non-protein Nitrogen (mg. %)	Length of Therapy (days)	Mean Dosage Hexamethonium Chloride (gm./day)	Maximum Dosage Hexamethonium Chloride (gm./day)	Mean Diastolic Pressure at Home (mm. Hg)
<i>Individual Patients</i>									
52, W, ♂	0	Moderate	0	141	30	92	See Figure 5		...*
47, W, ♂	0	Moderate	0	150	30	53	2.6	5.0	128
48, N, ♂	0	Slight	0	135	35	352	1.7	5.0	102
55, W, ♂	0	Advanced	0	125	39	53	2.8	3.8	88
55, N, ♂	0	Slight	0	171	40	68	1.7	3.8	96
52, N, ♀	0	Moderate	0	140	41	155	4.0	3.8	89
32, W, ♀	0	Advanced	0	160	42	31	6.3	6.3	...*
49, N, ♂	0	Advanced	0	150	67	40	3.4	6.0	112
33, N, ♂	0	Advanced	0	140	16	115	4.3	6.0	111
<i>Group Means</i>									
9 patients	0	×	0	146	38	107	3.7	5.5	104
6 patients	0	×	×	154	60	201	1.3	2.9	...†
5 patients	0	0	..	144	47	97	2.8	3.5‡	...†
28 patients§	×	0	0	144	39	649	2.6	3.9	94
maximum	×	0	0	176	64	1,469	7.5	12.5	114
minimum	×	0	0	121	30	121	1.0	1.3	74

* First and seventh patients were not discharged from the hospital.

† Only five of eleven patients in the two groups went home.

‡ Pentolinium tartrate 2.5 gm. orally in one patient was equated to 12.5 gm. hexamethonium chloride to obtain the group mean.

§ These are living patients. The lines designated maximum and minimum indicate the extreme variations for this group.

tachypnea and fibrinous pneumonitis which presumably resulted from methonium therapy. The characteristic pulmonary changes have only been observed in one non-azotemic patient. This man had albuminuria, hemorrhagic retinitis and a fixed diastolic pressure of 140 mm. Hg. Although recently a patient may have survived pulmonary disease complicating methonium therapy (Case II), the entity seems to have become increasingly rare; the absence of recent reports emphasizes the peculiar temporal grouping of our cases in 1951 and 1952.

Methonium-treated patients died with less nitrogen retention but with more fibrinous pneumonitis than untreated patients, suggesting that extensive and prolonged ganglionic blockade may protect the kidneys but sometimes is associated with damage to the lungs. The rarity of fibrinous pneumonitis in patients with mitral

stenosis argues against increased pulmonary venous pressure secondary to left heart failure as the important etiologic factor. Diminished gaseous exchange between alveoli and pulmonary capillaries, "alveolar-capillary block,"¹⁴ was considered compatible with the marked increase in the minute volume of respired air in the presence of a normal carbon dioxide content, pH and oxygen saturation of the blood. Advanced fibrinous pneumonitis might well cause considerable interference with gaseous exchange, with resultant tachypnea. The relatively good electrolyte balance gave no indication of a peripheral chemical mechanism for the extreme tachypnea. Similarly, the relatively normal circulation time and venous pressure, coupled with a lack of physical signs of pulmonary edema, argue against congestive failure as the principal cause of tachypnea. Mental

confusion that was prominent during the last hospitalization of the one living (Case II) and three dead patients raises the possibility of central nervous system dysfunction involving the respiratory center.

SUMMARY

In eight non-uremic patients with malignant hypertension and moderate azotemia who were treated with ganglionic blocking agents and hydralazine, extreme tachypnea developed. On postmortem examination they were found to have fibrinous pneumonitis resembling so-called "uremic pneumonia." Pyrexia, relative tachycardia and leukocytosis, without uremia, alkalosis or hyponatremia, characterized their terminal clinical episode. Previous control of the hypertension had been poor, with high average diastolic pressures and extreme fluctuations in systolic pressure despite large doses of ganglionic blocking agents.

The microscopic pulmonary lesions were studied in twenty-seven patients with a primary anatomic diagnosis of arteriolar nephrosclerosis who had received methonium salts and in sixty-seven such patients who had not been treated. Fibrinous pneumonitis was (1) significantly more frequent in methonium-treated patients than in untreated patients, (2) qualitatively similar anatomically in these two groups of patients, and (3) rare in non-uremic patients except those treated with hexamethonium. Fibrinous pneumonitis was not pronounced in any of the thirty-nine patients with mitral stenosis who also were studied; this tends to eliminate increased pulmonary venous pressure secondary to left heart failure as an important pathogenetic factor.

These data suggest that methonium salts may exert effects similar to those of the nitrogen retention products of the uremic state in the pathogenesis of fibrinous pneumonitis.

CASE REPORTS

CASE I. Other than asymptomatic hypertension for twenty-five years, this fifty-two year old white man was well until transient episodes of confusion began in January, 1954. At this time his blood pressure was 230/130 mm. Hg. Three months later severe dyspnea and hemoptysis accompanied myocardial infarction, at which time he was normotensive with a rectal temperature of 38.3°C. and a tachycardia of 140 beats per minute; a pericardial friction rub and auricular fibrillation appeared. To correct an anemia of 3.5 million erythrocytes per cu. mm. blood, two

transfusions were given. Hematuria and generalized edema followed. In the subsequent months unsuccessful attempts were made to control the blood pressure with small doses of reserpine, hydralazine and hexamethonium chloride. Surgical sympathectomy proved of no avail. The kidneys and adrenals were grossly normal at operation.

He entered Barnes Hospital fully digitalized, complaining of vertigo, amblyopia, nausea, emesis and exertional dyspnea without edema or angina. Except for a blood pressure of 250/140 mm. Hg, the vital signs were within normal limits. The physical examination revealed episodic aphasia and confusion. Hemorrhagic and exudative retinitis with papilledema were found. The lungs were clear to percussion and auscultation. There was marked cardiomegaly. Except for 12.2 gm. hemoglobin per 100 ml. blood, the hemogram was normal. The urinary specific gravity was 1.012; there was 1 plus albuminuria, microscopic hematuria and cylindruria. There were 31 mg. non-protein nitrogen and 190 mg. of cholesterol per 100 ml. plasma. The circulating electrolytes were within normal limits. The electrocardiogram was interpreted as indicating a posterior myocardial infarction of uncertain date of onset, a small recent antero-septal infarction, left ventricular enlargement and digitalis effect. The roentgenogram of the chest revealed cardiomegaly and elongation of the aorta. The electroencephalogram showed a slow dysrhythmia and a diffuse slowing consistent with hypertensive encephalopathy. The fifteen-minute excretion of intravenously injected phenol red was 5 per cent. Non-hemolytic white staphylococcus as well as coliform and paracolon organisms were cultured from the urine.

Antihypertensive therapy, vital signs and cardiac failure during hospitalization are indicated in the accompanying chart. (Fig. 6.) The initial drop in blood pressure was accompanied by a striking increase in confusion and by disappearance of the orthopnea and pulmonary rales which had appeared on the first day in the hospital. Because of the mental changes the blood pressure was allowed to rise; however, left ventricular failure reappeared and persisted, despite oxygen therapy, until the hypertension was reduced with parenteral pentolinium tartrate.

Three weeks after admission a shaking chill followed intravenous administration of fluids and the rectal temperature rose to 39.4°C. There was no concomitant cough, chest pain, headache or dysuria. Physical findings included a few rales at the bases of both lungs without signs of consolidation and abdominal distention without pain or tenderness. Initially there were only 5,500 leukocytes per cu. mm. of blood; twenty-four hours later there were 9,800. Roentgenograms of the chest were unchanged from the admission films. Blood and urine cultures were negative. Following seventy-two hours of penicillin and streptomycin therapy the temperature returned almost to normal.

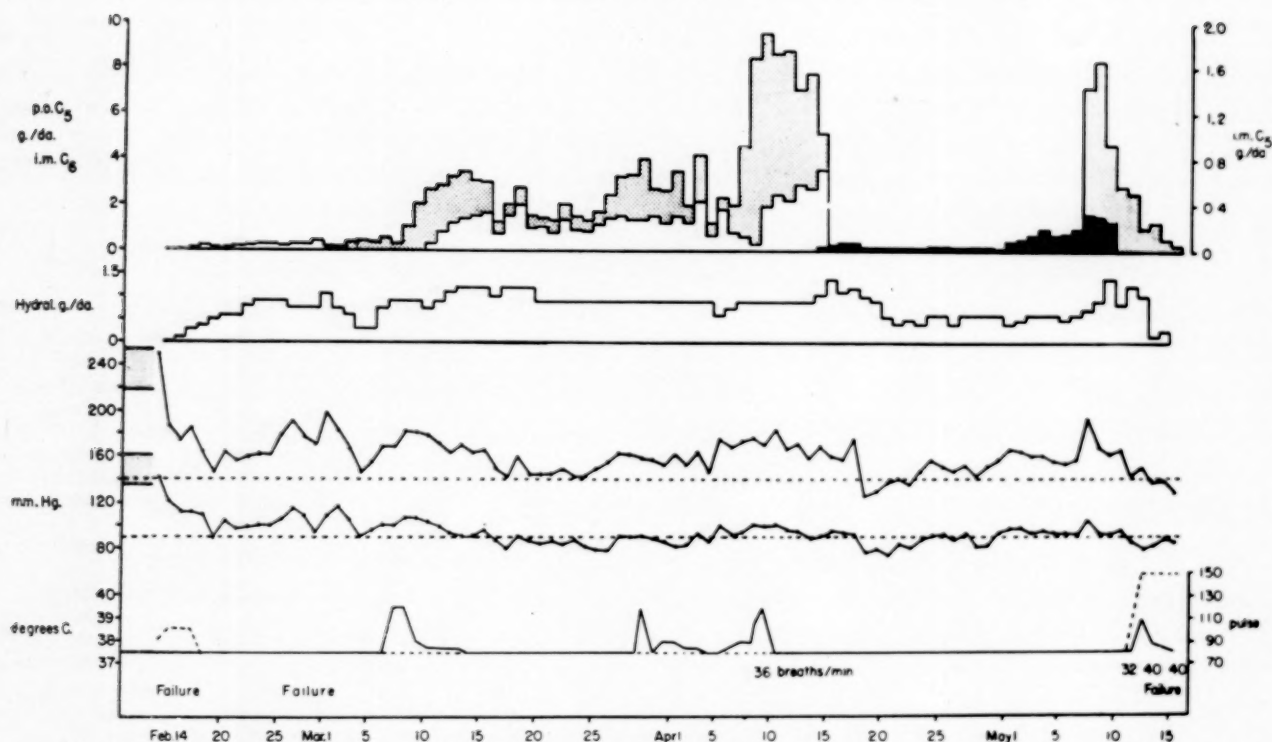


FIG. 6. Case I. Medication and vital signs during hospitalization of a fifty-two year old white man with malignant hypertension and pretreatment azotemia. The upper bar graph indicates the daily dose of autonomic blocking agent. The open bars represent oral pentolinium tartrate (po C₆). The stippled bars represent parenteral pentolinium tartrate (im C₆) and the solid bars represent parenteral hexamethonium chloride (im C₆). The potency of oral pentolinium tartrate approximates that of intramuscular hexamethonium chloride; however, the scale for intramuscular pentolinium tartrate has been expanded to allow for its greater effect. The lower bar graph indicates oral hydralazine intake per day. Line graphs show daily blood pressure averages, each point being the mean of at least six and often as many as twenty-four readings taken with the patient in a sitting position. The stippled area to the left indicates the pretreatment range of blood pressure. At the bottom of the figure is a schematic representation of the vital signs. The solid line shows the temperature in degrees centigrade which was always below 37.5 except for three bouts of pyrexia. The dotted line shows the pulse in beats per minute which was always below 80 except for two episodes of tachycardia. The figures indicate tachypnea, any daily average values above 30 breaths per minute being noted. The word *failure* denotes the three periods of cardiac decompensation.

Six weeks after entering the hospital a similar episode of fever reaching 39.6°C. without localizing signs or leukocytosis followed insertion of a retention catheter; however, coliform organisms were found in the urine and antibiotics were given. The temperature remained slightly elevated for ten days and then rose once more to 39°C. before subsiding. During this febrile episode the blood pressure became resistant to blocking agents. When the systolic elevation persisted despite large doses of pentolinium tartrate, administration of hexamethonium chloride was begun with an initially striking hypotensive effect; but within a month the development of tolerance was evident. After the second bout of fever, confusion and apathy became permanent and gradually increased, making tube feedings mandatory. The progressively worsening nutritional state was accompanied by a terminal cholesterol of 100 mg. per 100 ml. plasma but none of the stigmata of hydralazine toxicity such as arthritides or positive serum cephalin-cholesterol flocculation test

was noted. Ninety-six hours before death the temperature again suddenly rose to 39.4°C. accompanied for the first time by a leukocytosis of 25,000 white cells per cu. mm. blood. There was no physical or roentgenographic evidence of pulmonary disease. All cultures were negative except for the persistent confluent coliform growth from the urine. The terminal episode was characterized by a tachycardia of 145 and extreme air-hunger not adequately reflected by the respiratory rate.

Throughout the hospital course there were thirty-eight estimations of azotemia; the maximum value of 58 mg. non-protein per 100 ml. plasma was obtained the day before death. None of forty-two determinations of circulating sodium was below 120 mEq./L. of serum and only a pair of values, on May 5 and 7, was below 125 mEq. In thirty-two determinations the carbon dioxide content of venous plasma ranged from 21 to 34 mEq./L.

Marked arteriolar nephrosclerosis with bilateral foci

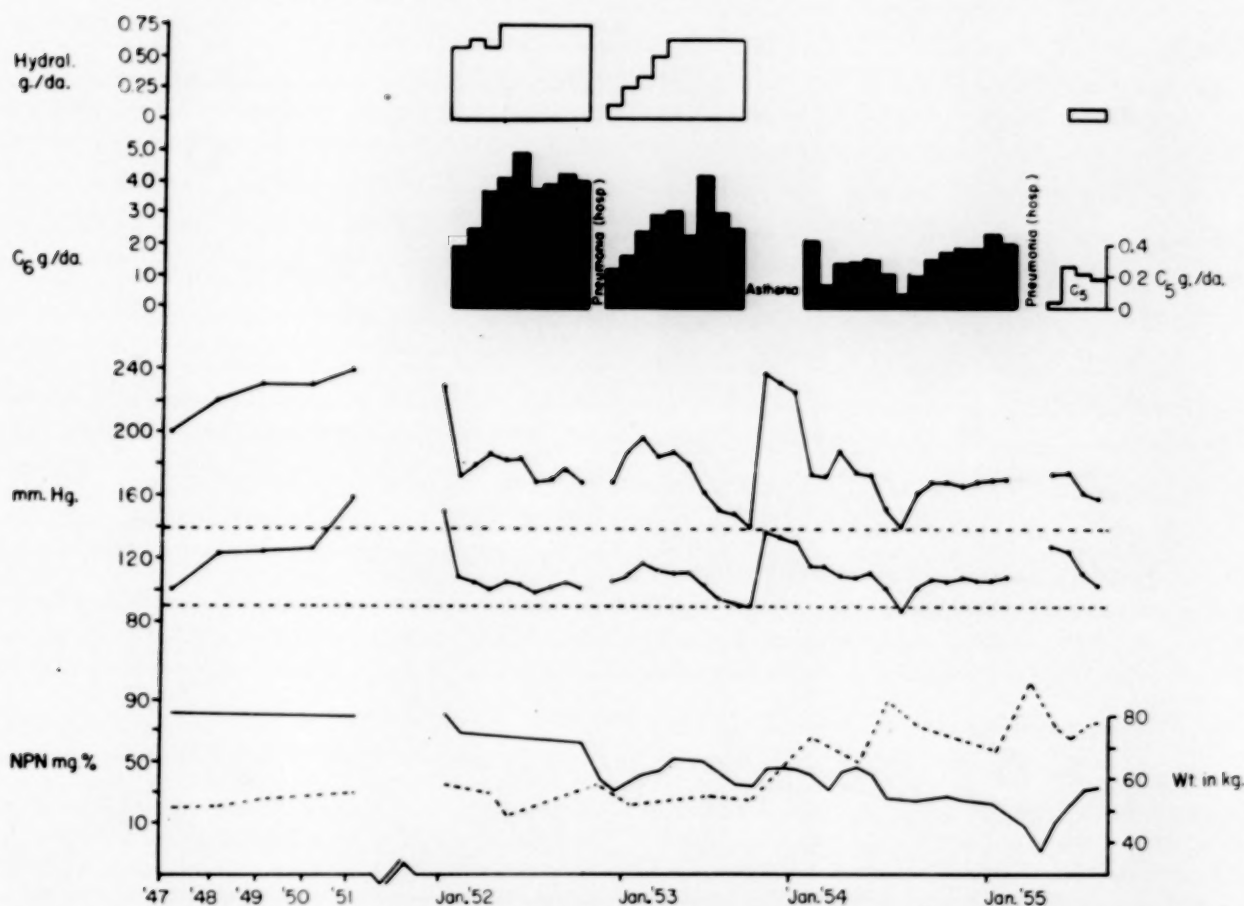


FIG. 7. Case II. Medication, blood pressure, weight and azotemia from 1947 in a forty-nine year old Negro housewife with malignant hypertension and pretreatment azotemia. The upper bar graph indicates the daily oral hydralazine intake. The lower one indicates the daily oral dose of two autonomic blocking agents, solid bars representing hexamethonium chloride (C_6) and open bars representing pentolinium tartrate (C_5). To reflect the greater potency of pentolinium tartrate its scale has been expanded. The medication is not indicated during any of the hospitalizations. Each bar indicates a monthly average and is calculated from the recordings of approximately 150 doses that the patient took at home. The upper line graph indicates blood pressure. To the left are the averages of all readings made on hospital and clinic visits during each of the five years she was followed up before therapy. In order to indicate further the level of pretreatment blood pressure, the average of the twenty supine determinations taken in the hospital by nurses is shown immediately before therapy was begun. Thereafter the graphed blood pressures are monthly averages, each value being the mean of 150 readings taken by the patient in the sitting position at home. At the bottom of the graph on the same time scale, weight is indicated by a solid line and azotemia by a dotted line; all values obtained in hospital or clinic from 1947 to the present are included.

of healed pyelonephritis was found at autopsy. The heart weighed 560 gm., and there was fibrosis in the anterior interventricular septum. Advanced arteriosclerosis of the coronary and cerebral arteries was evident. There was moderate arteriosclerosis of the pulmonary arteries, and congestion and edema of the lungs; a small depigmented infarct was present in the right upper lobe. In the pleural cavities there was 500 ml. of fluid; 100 ml. were found in the peritoneal cavity and 25 ml. in the pericardial cavity. Microscopic examination of the lungs revealed advanced edema. In addition, there were widely separated small foci in which the alveoli were filled with strands of fibrin, with beginning fibroblastic proliferation into an occasional fibrin mass. Nearby were areas, totaling

approximately one-fourth of the pulmonary tissue studied, in which dense hyaline membranes lined the walls of alveolar ducts and atria. In the areas containing hyaline membranes the alveolar ducts were often greatly distended and the alveoli collapsed. (Fig. 4.) No polymorphonuclear leukocytic exudation was present.

CASE II. The antihypertensive therapy, blood pressure, azotemia and weight of this forty-nine year old Negro housewife are indicated in Figure 7. She was first admitted to Barnes Hospital in 1947 when radon seeds were implanted and a radical neck dissection was performed following removal of a squamous cell carcinoma of the tongue. Thereafter a

benign cervical polyp was unsuccessfully treated with roentgenological castration. She was readmitted in January, 1952 because of progressive exertional dyspnea, pedal edema, amblyopia, headaches and worsening angina pectoris for which she had taken nitroglycerine for three years. On entering the hospital her vital signs were normal except for a blood pressure of 214/160 mm. Hg. The significant physical findings were hemorrhagic and exudative retinitis with minimal papilledema and cardiomegaly with a greatly accentuated second aortic sound. The lungs were clear to percussion and auscultation; there was no pedal edema. Pertinent laboratory data included an essentially normal hemogram with 4.11 million erythrocytes and 5.05 thousand leukocytes per cu. mm. blood. There was 3 plus albuminuria with cylindruria but no hematuria. The maximum urinary specific gravity was 1.013; 10 per cent of intravenously injected phenol red was excreted in fifteen minutes. The urine culture was sterile. There were 35 mg. of non-protein nitrogen, 377 mg. of cholesterol, 4.0 gm. of albumin, and 3.5 gm. of globulin per 100 ml. plasma. The electrocardiogram and roentgenogram of the chest were interpreted as indicating left ventricular hypertrophy. Benzodioxine produced an immediate increase in blood pressure of 40/20 mm. Hg, while the minimum level following sodium amytal was 160/100 mm. Hg. With 100 mg. hydralazine and a variable dose up to 500 mg. hexamethonium chloride every four hours the mean blood pressure fell to 150/100 mm. Hg without noticeable effect on the slight azotemia.

She was sent home with instructions to continue this combined therapy but in order to maintain a diastolic pressure average of about 100 mm. Hg it was necessary to increase the medication until her daily hexamethonium intake was doubled. In November, 1952 when she was readmitted following an episode of syncope, she complained of increasing dyspnea for six weeks plus a tight substernal ache on coughing. Asthenia was prominent. The pulse was 120 beats per minute, the temperature was 37.8°C., the blood pressure was 200/104 mm. Hg, and the respiratory rate was 60 breaths a minute. Other abnormal findings included a diastolic gallop and dullness to percussion with fine rales over the left base. The marked tachypnea was improved by the supine position. Funduscopic examination revealed no hemorrhages, exudates or papilledema. No significant neurologic changes or peripheral edema was present. There were 5.20 million erythrocytes and 10.5 thousand leukocytes per cu. mm. blood. Cylindruria and 3 plus albuminuria had persisted; the urinary pH was below 5.0. There were 36 mg. non-protein nitrogen, 14.2 mEq. sodium, and 2.88 mEq. of carbon dioxide per 100 ml. plasma. The arm-to-tongue circulation time using decholin was fifteen seconds and the venous pressure measured 110 mm. saline solution. A roentgenogram of the chest was interpreted as show-

ing a marked infiltrative process in the left lung with fluid at the base. The electrocardiogram was thought to show right bundle branch block and posterior myocardial ischemia. A pair of needle biopsies of the lung were unsuccessful and bronchoscopy contributed nothing. Cephalin-cholesterol flocculation of the serum was negative and the thymol turbidity was 3.4 units. Oxygen, streptomycin, penicillin and digitalis were now given in addition to the continuing hexamethonium and hydralazine therapy. Twice during the first week in the hospital the temperature was 38.5°C. but thereafter it remained below 38°C. with both pulse and respiratory rate gradually falling to normal. The blood pressure was controlled at about 165/105 mm. Hg with almost no hydralazine and less than a fourth of the prehospital intake of blocking agent.

In August, 1953 the patient, who had been doing well at home on large doses of hydralazine and hexamethonium chloride, returned to the clinic with anorexia, a weight loss of 6 Kg. in six weeks, generalized malaise and asthenia so severe that she could not sit upright. Her pulse was 88 beats per minute; her temperature was 37.5°C., her respirations were 19 breaths per minute; and her blood pressure was 140/90 mm. Hg. Funduscopic examination revealed no hemorrhages, exudates or papilledema. There was dullness over the bases of both lungs, without rales. Cardiomegaly and a diastolic gallop were noted. The liver edge was palpable 3 cm. below the right costal margin for the first time. No edema was noted. There were 4.85 million erythrocytes per cu. mm. blood but only 3.20 thousand leukocytes of which 66 per cent were neutrophilic granulocytes and 34 per cent lymphocytes. There was 2 plus albuminuria, microscopic hematuria, and cylindruria; the urinary pH was 5.0. The corrected sedimentation rate was 44 mm. per hour. Roentgenogram of the chest revealed hilar adenopathy as well as the previously noted cardiomegaly and pneumonitis with pleural effusion. There were 30 mg. of non-protein nitrogen per 100 ml. plasma; the hyperglobulinemia had persisted unchanged. Neither the serum cephalin-cholesterol flocculation nor the thymol turbidity test was positive, although six months later the former was 2 plus and the latter 8.5 units at a time when the azotemia had increased to 94 mg. non-protein nitrogen and the hyperglobulinemia to 4.1 gm. of globulin per 100 ml. plasma. Within five days of discontinuing both hydralazine and hexamethonium chloride there was an obvious increase in strength and during the subsequent six weeks she regained 5 Kg; however, her normotension was replaced by a mean blood pressure of 200/139 mm. Hg which, in combination with recrudescence of hemorrhagic and exudative retinitis, forced reinstitution of hexamethonium therapy at the end of four months.

The patient reentered Barnes Hospital in March, 1955 because of incapacitating dyspnea which had

been increasing for a month. She was completely disoriented and cachectic. Her pulse was 120 beats per minute, her temperature 38.2°C., her blood pressure 150/70 mm. Hg, and she was taking 64 breaths per minute. Her pupils were dilated and reacted sluggishly; funduscopic examination revealed old exudates. Rales were present throughout both lung fields and there was dullness in the right base. The pulse was regular and there was no gallop; the cardiomegaly was unchanged. Ankle jerks were not elicited and pathologic toe signs were present bilaterally; the neurologic examination was not otherwise remarkable. No peripheral edema was noted. There were 2.66 million erythrocytes per cu. mm. blood and 13.0 thousand leukocytes with a normal differential. Microscopic hematuria and cylindruria persisted along with 2 plus albuminuria. The urine consistently was very strongly acid. The corrected sedimentation rate was 68 mm. per hour. There were 68 mg. non-protein nitrogen, 134 mg. cholesterol, 3.3 gm. albumin, 3.2 gm. globulin, 14.7 mEq. sodium, and 1.87 mEq. carbon dioxide per 100 ml. plasma. The partial pressure of carbon dioxide in arteriolar blood was 23.5 mm. Hg and its oxygen saturation was 98 to 100 per cent; the pH of the blood was 7.39. The venous pressure was 45 mm. of saline solution on two occasions. A roentgenogram of the chest (Fig. 8) was interpreted as advanced generalized carcinomatosis, although the clinical picture suggested fibrinous pneumonitis. The electrocardiogram revealed right bundle branch block. No bacteria could be grown from blood or urine; however, non-hemolytic streptococci were cultured from the throat. The thymol turbidity of the serum was 4.8 units and there was no cephalin-cholesterol flocculation. Several L.E. preparations were negative. The cerebrospinal fluid was not remarkable. The electroencephalogram was not helpful and showed no clear focalization or lateralization suggestive of organic brain damage but the patient remained helpless and disoriented. Cortisone was given along with antibiotics and oxygen. During the first four days in the hospital leukocytosis, tachycardia, pyrexia and azotemia increased to maximum of 16 thousand cells per cu. mm. blood, 145 beats per minute, 39.2°C., and 103 mg. per 100 ml. plasma respectively. During this period the blood pressure was very variable, averaging 190/95 mm. Hg without any blocking agent. Six weeks after entering the hospital the patient was discharged completely oriented and without fever, tachycardia or dyspnea. She had 87 mg. non-protein nitrogen per 100 ml. plasma and her mean blood pressure was 140/80 mm. Hg with only occasional doses of pentolinium tartrate.

At present, forty-eight months after she was first treated for malignant hypertension with azotemia, she is alert and does all her housework without symptoms. She has 3.65 million erythrocytes and 5.25 thousand leukocytes per cu. mm. blood. Her urinaly-

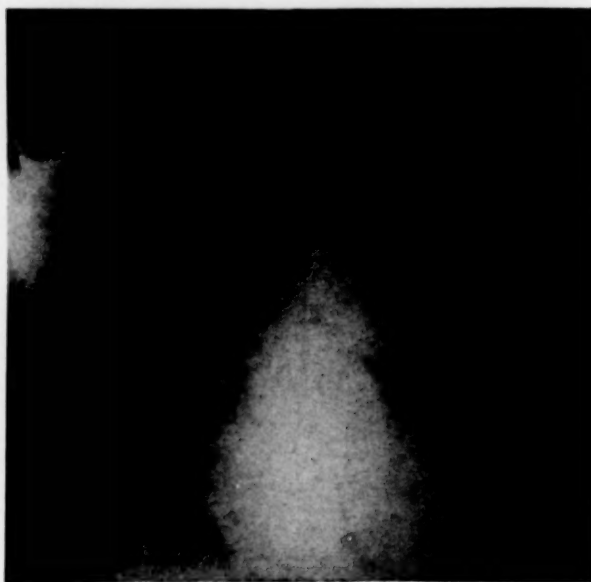


FIG. 8. Case II. Roentgenogram of chest on March 13, 1955, the day of last admission to hospital, showing the diffuse patchy infiltration seen in fibrinous pneumonitis.

sis is unchanged. Her renal function is very poor as indicated by persistent azotemia and less than 10 per cent excretion of intravenously injected phenol red in 120 minutes. There has been no further evidence of pulmonary disease. Her hyperglobulinemia has vanished and her hepatic function is apparently normal.

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Clinical Determination of the Diffusion Capacity of the Lungs*

Comparison of Methods in Normal Subjects and Patients with "Alveolar-Capillary Block" Syndrome

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THE concept of dyspnea and disability due to impaired mechanics of breathing is well accepted. Relatively simple tests for measurement of ventilatory function are generally understood and their limitations appreciated. Such studies are now widely used for routine diagnostic screening, for clinical evaluation and for assessment of medical and surgical therapy.

It has been known for many years that dyspnea of pulmonary origin can occur in the absence of gross abnormalities in the mechanics of breathing [1,2,3]. This has been attributed to an alteration of the "alveolar-capillary membrane" impeding the exchange of oxygen through the tissues separating the alveolar air from the hemoglobin within the pulmonary capillary erythrocytes. Although the mechanism of this transfer was a subject of considerable controversy early in this century it is now generally accepted to be one of simple diffusion. Quantitation of the effectiveness of this gas exchange requires determination of the diffusion capacity (D) of the lungs which is defined as follows:

quantity of gas transferred across the membrane (oxygen uptake) and the oxygen pressure difference between the alveolar air and the pulmonary capillary blood were known. The inaccessibility of pulmonary capillaries for sampling has made direct pressure measurement impossible. However, the peripheral arterial blood is readily available and the pressure difference between alveolar air and arterial blood, the so-called "A-a gradient," may be determined. The failure of arterial blood to attain nearly the same O₂ tension as the alveolar gas has led to the realization that the observed A-a gradient consists of a "membrane" component due to the diffusion process and a "venous admixture" component due to the appearance in the peripheral arteries of blood which has not been in contact with alveolar gas. In 1942 Berggren [4] suggested that separation of venous admixture from diffusion gradients might be obtained by altering the concentration of the oxygen in the inspired air. Lilienthal et al. [5] and Riley et al. [6] devised a method for calculating the diffusion capacity

$$D = \frac{\text{Volume of gas diffusing across membrane per unit of time}}{\text{Mean difference in pressure of gas between two sides of membrane}} \quad (1)$$

and is usually expressed in cc. per minute per mm. of mercury. Therefore, the diffusion capacity for oxygen could be determined if the

for oxygen (D_{O₂}) using the alveolar-arterial oxygen pressure differences determined at two different levels of oxygenation. At the higher

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level, usually room air, the difference is due primarily to venous admixture, whereas at the lower level the measured pressure difference reflects the permeability of the membrane. Under certain rigidly controlled conditions the graphic integration of these two-level A-a gradients allows the calculation of the D_{O_2} . The problems of maintaining the stringent conditions required and the technical difficulties of direct determination of arterial gas tensions have limited the clinical applicability of this technic.

Krogh [7], in 1915, noting the greatest difficulty in direct measurement of D_{O_2} , namely the necessity for determination of the end-capillary O_2 pressure, substituted carbon monoxide as the test gas. Because of its affinity for hemoglobin, which is 200 to 250 times greater than that for O_2 , it was assumed that carbon monoxide (CO) is removed rapidly and completely from the dissolved state in the plasma and therefore exerts no appreciable "back pressure" in the pulmonary capillary blood. Under these circumstances equation (1) is simplified to: volume of gas diffused per unit of time/alveolar pressure of gas.

Recently, there has been renewed interest in the use of CO for evaluation of diffusion. Filley *et al.* [8] described a method for the determination of the diffusion capacity for carbon monoxide (D_{CO}) during the steady state. It is assumed here, as in the direct D_{O_2} method, that there is no gradient between alveolar and arterial carbon dioxide (CO_2). Since the dead space for CO is the same as that for CO_2 , the alveolar (= arterial) pressure of CO_2 is substituted in the Bohr dead space equation for calculation of the mean alveolar CO tension. The D_{CO} can then be calculated according to equation (1) because the alveolar CO tension is now known, the pulmonary capillary CO tension is assumed to be zero, and the CO uptake can be determined easily from inspired and expired CO concentrations.

The single breath CO method of Forster *et al.* [9] is a modification of the original method of Krogh. A maximal inspiration is made of a mixture of CO and helium (He) in air, the breath held for ten seconds and then an alveolar sample is collected. The physiologically inert He is used to calculate the alveolar concentration of CO before any diffusion of this gas through the membrane has occurred.

These two methods appear to offer relatively simple measures for the diffusion capacity of

the lungs. The D_{CO} can be expressed in terms of D_{O_2} since O_2 is known [10] to be 1.23 times more diffusible than CO.

This study was undertaken, first, to compare the D_{CO} obtained by these two methods and, if possible, to relate the D_{CO} to the fraction of CO removed [11]; second, to establish normal values and to relate these to data from a group of patients in whom an impairment in the transfer of O_2 appeared to be the major physiologic defect; and, third, to compare these D_{CO} values with the directly determined D_{O_2} .

METHODS

Conventional Ventilatory Function Studies. These included triplicate determinations of maximal breathing capacity by the open-circuit method; vital and 1, 2 and 3 second timed vital capacities by an electronically timed dial spirometer [12]; measurements in duplicate of residual volume and of intrapulmonary mixing index by a modified open circuit nitrogen washout technic [13] and determination of subdivisions of the vital capacity, minute ventilation, oxygen consumption and ventilation equivalent for oxygen by closed circuit spirometry. All volumes except O_2 uptake were expressed at BTPS. Details of the methods and modifications used in our laboratory have been reported previously [13]. Predicted normal performance for maximal breathing capacities and lung volumes were calculated according to the regression equations of Baldwin *et al.* [14].

Appraisal of Diffusion. D_{O_2} (Steady State): The technic and calculations followed closely those of Riley *et al.* [6]. With the patient supine, breathing room air, the brachial artery was cannulized. Thirty minutes were allowed for attainment of a steady state. Expired air and arterial blood were then collected simultaneously during a three-minute interval. The expired air was analyzed for O_2 and CO_2 with the Scholander apparatus with duplicate determinations required to check within 0.02 per cent. The arterial O_2 tension (P_{O_2}) and CO_2 tension (P_{CO_2}) were measured in duplicate by a modified bubble equilibration technic [15] with 2 mm. checks required. Arterial O_2 and CO_2 contents and O_2 capacities were determined manometrically. The arterial pH was measured anaerobically at room temperature with a glass electrode and corrected to body temperature. The P_{CO_2} was also calculated by nomogram [16] from the determined CO_2 content and pH and was compared with the directly obtained value. The mean alveolar P_{O_2} was calculated according to the alveolar equation [5] and the alveolar-arterial O_2 difference or A-a gradient determined. The entire procedure was then repeated using a low O_2 concentration in the inspired gas. The O_2 percentage was selected so that the arterial saturation would be at the beginning of the steep portion of

the O_2 dissociation curve. In a few instances the patient's arterial saturation during room air breathing was already in that range and a gas with a higher, rather than lower, O_2 concentration was then required for the second determination. These two A-a gradients were then graphically integrated and, whenever possible, the mean pulmonary capillary O_2 tension established. From this tension, the simultaneously measured O_2 uptake, and the calculated alveolar P_{O_2} , the DO_2 was determined.

D_{CO} (Steady State): The procedure suggested by Filley et al. [8] was followed except that infra-red CO analysis* was substituted for the chemical method. With the brachial artery needle in place the patient breathed room air at rest for fifteen to twenty minutes. An inspired gas containing approximately 0.1 per cent CO was then substituted. The O_2 concentration of this gas was adjusted to that of room air to avoid altering the steady state. A four-minute interval was allowed for equilibration of the lungs with the inspired gas and to flush the expired air circuit and collecting bag. Arterial blood and expired air were then sampled simultaneously over a three-minute period, the fifth through the seventh minutes of CO breathing. The relative concentrations of CO in the inspired and expired gases were measured with the infra-red gas analyzer and expressed in absolute CO concentrations by reference to standard gases analyzed to one part per 100,000. The minute uptake of CO was determined from these analyses and from the minute volume of expired gas. The arterial P_{CO_2} was measured as in the DO_2 method. By substitution of the arterial P_{CO_2} in the Bohr dead space equation the mean alveolar P_{CO} was calculated. The diffusion capacity for CO could then be calculated, assuming that the partial pressure of CO in the pulmonary capillary blood is zero.

Fraction of CO Removed (F_{CO}): From data obtained during the steady state D_{CO} procedure an additional index of CO diffusion was calculated. This F_{CO} was considered by Bates [11] an estimate of the ventilation of perfused lung tissue and hence a reflection of diffusion. The F_{CO} was obtained by dividing the measured CO uptake by the amount of CO presented to the lungs. We modified this method slightly by using the determined physiologic, rather than the apparatus, dead space alone, in effect calculating the fraction of CO removed from the alveolar ventilation rather than total ventilation [8].

D_{CO} (Single Breath): The procedure suggested by Forster et al. [9] was followed. With the patient seated, breathing room air, a forced expiration was followed immediately by a maximal inspiration of a gas containing approximately 0.3 per cent CO, 10 per cent He, 20 per cent O_2 and 70 per cent N_2 from a box-balloon system allowing simultaneous recording of the

inspired volume. The breath was held for exactly ten seconds and then rapidly exhaled. The last 500 cc. of expired gas, or "alveolar" sample, was analyzed for CO and He. The ratio of expired to inspired He concentrations was a measure of the degree of dilution of the inspired gas by residual volume and anatomic and apparatus dead space, presuming that He is not taken up by the tissues. This ratio was used to calculate the initial alveolar concentration of CO before any diffusion has occurred. The final concentration of alveolar CO in the collected alveolar sample was measured by infra-red analysis and the D_{CO} calculated.

At least three hours were allowed to elapse between the steady state and single breath D_{CO} determinations to minimize any effect of retained CO.

SELECTION OF PATIENTS

Only patients who fulfilled our criteria of "alveolar-capillary block" syndrome were included in this report. These criteria were: (1) diffuse, finely dispersed parenchymal lesions by roentgenogram, (2) normal ventilatory function or dyspnea out of proportion to the measured ventilatory defect, (3) impairment of diffusion capacity, and (4) absence of physiologic evidence of obstructive emphysema. The last condition was imposed because one of the methods, the D_{CO} single breath technic, is based on alveolar sampling which is not reliable in patients with serious distributional defects. Also, under these circumstances the calculation of alveolar gas concentrations and the use of the Bohr dead space equation may not be valid. In keeping with the purpose of this study an additional requirement was available data of resting diffusion capacity by at least two methods.

Thirteen normal volunteers recruited from the house staff and laboratory personnel were included as controls. This was necessary because of the paucity of information concerning normal values for the carbon monoxide methods. No attempt was made to estimate the direct DO_2 in the normal subjects since adequate studies in this regard have been published [17].

RESULTS

Thirty-one patients were studied on thirty-three occasions. Clinical data are listed in Table 1. Diagnoses included beryllium disease, sarcoidosis, chronic interstitial pneumonitis, silicosis, miliary tuberculosis, scleroderma and eosinophilic granuloma. In nine patients the diagnoses were based on clinical criteria alone. Tissue obtained by biopsy was available in twelve patients. This was lung in eight, scalene node in three and skin in one. In addition, *Mycobacterium tuberculosis* was cultured from bone marrow aspirate of one patient and gastric contents of another. Figures 1A through F are

* Gas analyzer Model-15, Liston-Becker Division of Beckman Instruments, Inc., 649 Hope Street, Springdale, Connecticut.

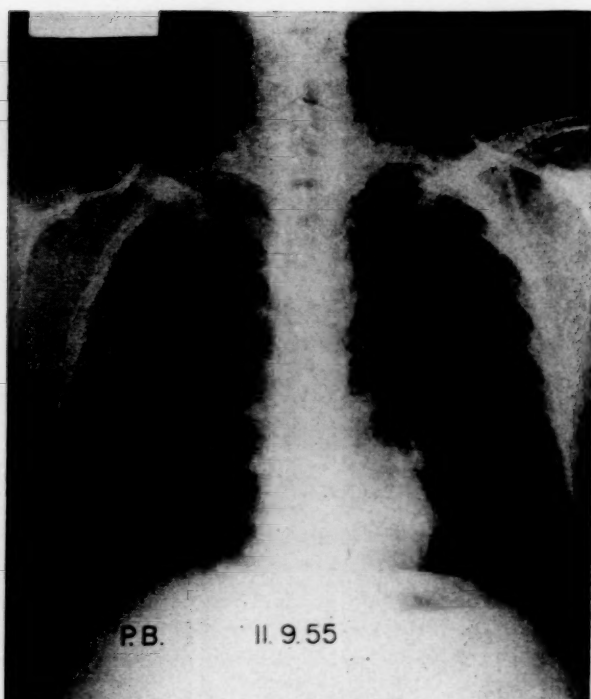


FIG. 1. A, Case 2. Patient P. B., a forty year old research engineer with beryllium disease.

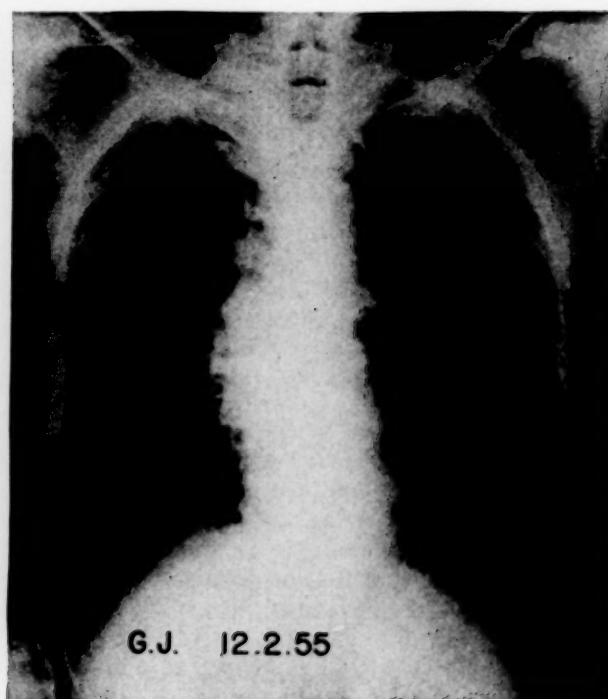


FIG. 1. B, Case 14. Patient G. J., a fifty-two year old cook with miliary tuberculosis.

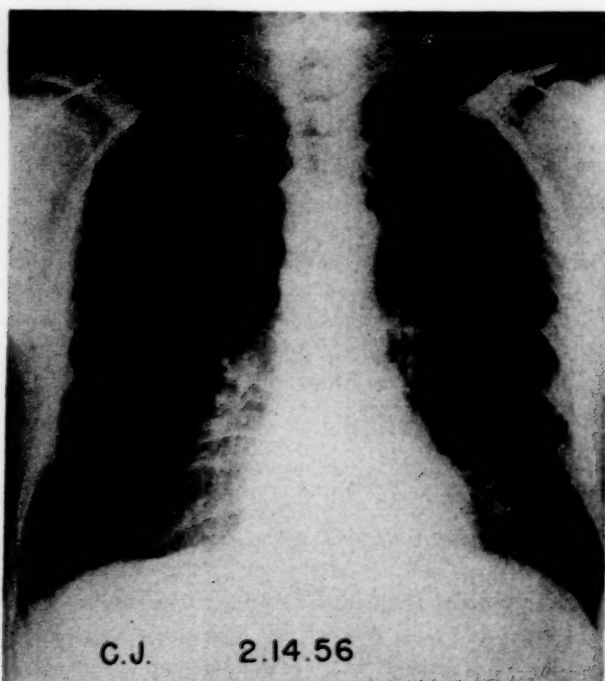


FIG. 1. C, Case 15. Patient C. J., a fifty-five year old ship engineer with pneumoconiosis who had worked in a stone quarry.

typical chest roentgenograms of patients with "alveolar-capillary block" syndrome. Dyspnea, the only symptom common to the group, ranged from minimal (+) to severe (++++) . Other

symptoms were quite variable. (Table I.) The known length of illness varied from a few months to many years. In general, most of our patients were in an early stage of their disease.

Results of conventional pulmonary function tests: These results obviously reflect our criteria of selection of patients. (Fig. 2 and Table II.) Average values for the group will be considered first. The maximal breathing capacity was 102 L./min. or 94 per cent of predicted and individual performances fell almost wholly within the predicted normal range [14] of 80 to 120 per cent. The maximal breathing capacity of the normal volunteers averaged 152 L./min. or 118 per cent. The vital capacity of the patients of 2.93 L. or 80 per cent was at the lower limit of the normal predicted but quite reduced when compared to our own normal subjects. The total lung capacity of 4.43 L. or 92 per cent was probably also slightly reduced when compared to the total lung capacity of the normal subjects of 6.00 L. or 118 per cent. The finding of a slight ventilatory insufficiency of the "restrictive" type in these patients with diffuse pulmonary fibroses and granulomatoses was not unexpected and has been previously described [18-20]. There was no evidence of "obstructive" ventilatory insufficiency. The one-second vital capacity of 75 per cent of the total and the residual volume of 1.41

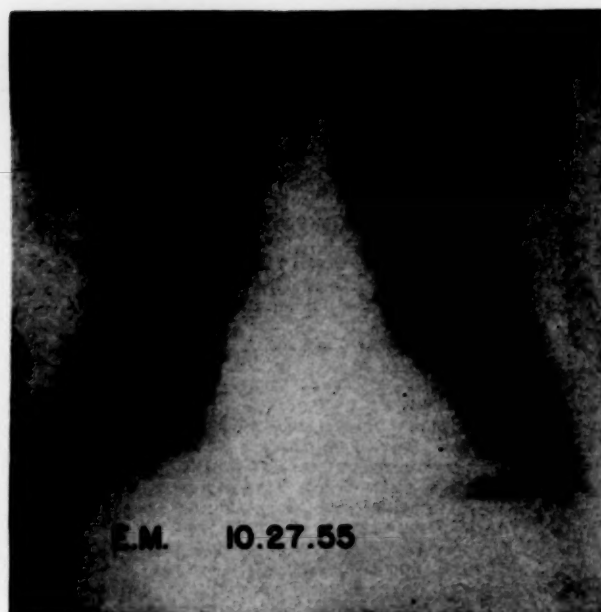


FIG. 1. D, Case 18. Patient E. M., a sixty year old coal miner in whom a biopsy specimen of the lung showed advanced silicosis.

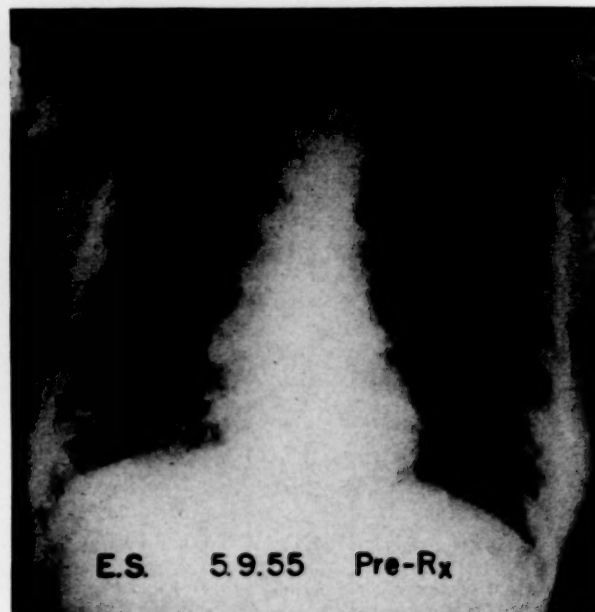


FIG. 1. E, Case 25A. Patient E. S., a thirty-seven year old housewife with sarcoidosis, before treatment.

L. or 117 per cent were within the normal range considering our normal subjects with a residual volume of 1.20 L. or 115 per cent. The residual volume/total lung capacity ratio of 31.5 per cent was slightly larger in comparison to 19.9 per cent for the normal volunteers. This was due to a reduction of the denominator rather than an increase of the numerator. The pulmonary mixing index of the patients of 1.48 per cent nitrogen was not greater than our own established upper limit of normal of 1.5 per cent nitrogen [13].

Consideration of individual results reveals a number of patients with quite marked restrictive ventilatory insufficiency; in all these cases the pulmonary complaints appeared to be more severe than could be explained on these grounds alone. Often, the dyspnea index was elevated but due more to a markedly increased ventilatory requirement than a reduced breathing capacity. The one patient with very severely disturbed mechanics of breathing (No. 28) also had more extensive pulmonary involvement than others (Fig. 1F) but, more important, the reported results were unusually poor because of his markedly retarded physical development with a stature corresponding to that of a normal nine year old child. Several other patients had a slight diminution of maximal expiratory velocity as determined by the one-second vital capacity. They were not excluded because the diagnosis

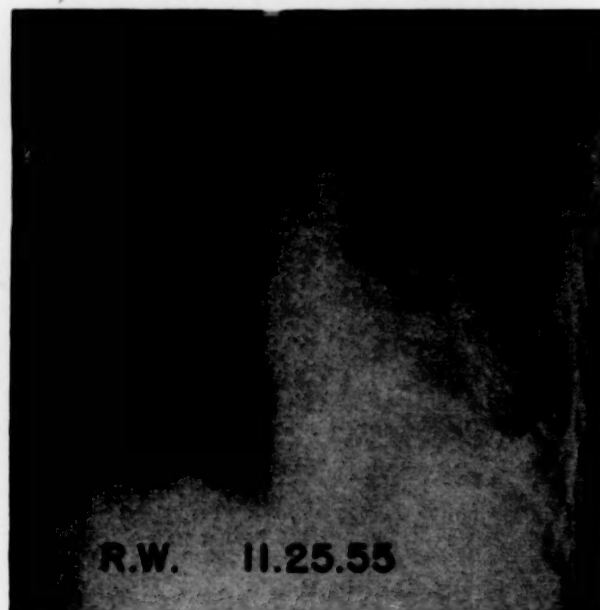


FIG. 1. F, Case 28. Patient R. W., a sixteen year old student with pulmonary scleroderma.

of obstructive emphysema was not supported by other ventilatory data and almost all patients had a greater impairment of vital capacity than of maximal breathing capacity, resulting in an air velocity index which was greater than 1.0. From the medico-legal standpoint emphasis should be placed on patients such as Nos. 8, 12, 13, 15 and 18 who complained of considerable dyspnea and yet had results of conventional

TABLE I
CLINICAL DATA

Case No.	Age and Sex	Occupation	Duration Symptoms	Dyspnea	Diagnosis	Method of Diagnosis	History*
1	39, M	Foundry worker	1 yr.	+	Interstitial pneumonitis	Lung biopsy	Forge cleaner and steel grinder (7 yr.); productive cough for 1 yr.
2	40, M	Research engineer	9 yr.	+	Beryllium disease	Epidemiologic	Fluorescent bulb worker (6 mo.) 14 yr. ago; abnormal x-ray, 9 yr.; slight dyspnea, 6 mo.
3	26, F	Housewife	1 mo.	0	Miliary tuberculosis	Bone marrow culture	Fever, weight loss and anorexia, 1 mo.
4	62, M	Policeman	1 yr.	+++	Pulmonary fibrosis	Clinical	Pneumonia, 13 yr. ago; angina pectoris, 10 yr.; progressive dyspnea and cough, 1 yr.
5	59, M	Unemployed	2 mo.	++	Pulmonary fibrosis	Clinical	Abnormal x-ray, 3 yr.; cough, anorexia, 1 mo.
6	58, M	Coal miner	5 yr.	+++	Silicosis	Lung biopsy	Coal miner (35 yr.); moderate dyspnea, 5 yr.
7	29, F	Housewife	4 yr.	++	Sarcoidosis	Scalene node biopsy	Dyspnea and cough following cold 4 yr. ago; no industrial exposure; cortisone, 1½ yr.
8	48, M	Machinist	6 yr.	++	Beryllium disease	Epidemiologic	Beryllium rod cutter (1 wk.) 9 yr. ago; hoarseness, fatigue, chest pain and weight loss, 6 yrs.; corticosteroid treatment, 5 yr.
9	48, M	Pipe fitter	2½ yr.	++	Pneumoconiosis ? asbestosis	Clinical	Covered pipes with asbestos and fiberglass (13 yr.); cough, abnormal x-ray, 2½ yr.
10	39, M	Foundry worker	2½ yr.	+++	Interstitial fibrosis	Lung biopsy	Foundry worker (6 yr.); cough, weight loss, tightness in chest, progressive dyspnea, 2½ yr.
11	18, M	College student	3 yr.	0	Sarcoidosis	Scalene node biopsy	Cough, nausea and abnormal x-ray, 3 yr.
12	38, F	Nurse	6 mo.	+	Sarcoidosis	Scalene node biopsy	Cervical adenopathy, 5 yr.; fatigue, migratory polyarthritides, weight loss and dyspnea, 6 mo.
13	36, M	Insurance salesman	6 mo.	+	Beryllium disease	Epidemiologic	Fluorescent bulb worker 15 yr. ago; cough, fatigability and minimal dyspnea, 6 mo.
14	52, M	Cook	6 mo.	0	Miliary tuberculosis	Gastric culture	Weight loss, occasional guaiac-positive stools, 6 mo.; Papanicolaou of bronchial aspirate Grade IV; scalene node: ? sarcoid
15	55, M	Ship engineer	6 mo.	+	Pneumoconiosis	Clinical	Stone quarry work (1 yr.) 20 yr. ago; abnormal x-ray, 6 mo.; minimal dyspnea
16	33, F	Receptionist	8 mo.	0	Beryllium disease	Epidemiologic	Fluorescent bulb coater (1½ yr.) 14 yr. ago; pleurisy and minimal dyspnea, 8 mo.
17	52, M	Manager, food store	4 yr.	+++	Pulmonary fibrosis	Clinical	Pneumonia 4 yr. ago; progressive dyspnea and slight cough since; no industrial exposure
18	60, M	Coal miner	5 yr.	+++	Silicosis	Lung biopsy	Coal miner (40 yr.); moderate dyspnea, 5 yr.
19	44, M	Draftsman	4 yr.	++	Beryllium disease	Lung biopsy and spectroscopic	Draftsman in beryllium factory (9 mo.), 13 yr. ago; cough, fatigue, cyanosis, clubbing, 4 yr.
20	26, M	Industrial researcher	5 yr.	++	Beryllium disease	Epidemiologic	Experimental beryllium grinding (3 mo.), 10 yr. ago; dyspnea, cough, chest pain, 5 yr.
21	69, M	Iron molder	6 mo.	++	Pulmonary fibrosis ? silicosis	Clinical	Molder in cast iron foundry (44 yr.); abnormal x-ray, 9 yr.; productive cough, dyspnea, 6 mo.
22A	27, M	Dairy farmer	4 yr.	+++	Eosinophilic granuloma	Lung biopsy	Abnormal x-ray, 4 yr.; progressive dyspnea, 4 yr. not altered by cortisone; spontaneous pneumothorax, 2 yr. ago; restudied after 1,500 r. to lung fields
22B	27, M	Dairy farmer	4 yr.	"	Eosinophilic granuloma	Lung biopsy	
23	36, F	Engineering technician	6 mo.	++	Beryllium disease	Epidemiologic	Fluorescent bulb plant worker (15 yr.); abnormal x-ray and progressive dyspnea, 6 mo.
24	23, M	Sailor	2 mo.	0	Sarcoidosis	Clinical	Cervical adenopathy, biopsy: normal lymph node; asymptomatic; no industrial exposure
25A	37, F	Housewife	3 mo.	++++	Sarcoidosis	Scalene node biopsy	Cough, blood-streaked sputum, chest pain and weight loss, 3 mo.; no industrial exposure; restudied after 1 mo. prednisone, clinically improved
25B	37, F	Housewife	3 mo.	++	Sarcoidosis		
26	32, M	Industrial worker	8 yr.	0	Beryllium disease	Epidemiologic	Fluorescent bulb worker (6 mo.), 15 yr. ago; weight loss, cough, moderate dyspnea, 8 yr.; asymptomatic on cortisone
27	24, M	Sailor	6 mo.	0	Interstitial pneumonitis	Lung biopsy	Exposed to petroleum fumes and paint dust (2 yr.), abnormal x-ray on discharge from service
28	16, M	Student	7 yr.	+++	Scleroderma	Skin biopsy	Retarded growth, abnormal x-ray and dyspnea, 7 yr.; recent cyanosis, clubbing, spontaneous pneumothorax
29	28, F	Housewife	2 yr.	++	Beryllium disease	Epidemiologic	Draftswoman in beryllium plant (3 mo.); weight loss, cough, dyspnea, abnormal x-ray, 2 yr.
30	47, F	Housewife	6 mo.	+	Pulmonary fibrosis	Clinical	Recurrent pneumonia, cough and blood-streaked sputum; no industrial exposure
31	40, F	Housewife	4 yr.	+	Sarcoidosis	Lung biopsy	Virus pneumonia, 4 yr. ago; clubbing, minimal dyspnea; no industrial exposure

* Duration of exposure in parentheses

TABLE II
VENTILATION

Case No.	Age and Sex	Body Surface Area (M ²)	Maximum Breathing Capacity (L./min.)		1 Second Timed Vital Capacity (% of total)	Air Velocity Index	Vital Capacity (L.)		Residual Volume (L.)		Total Lung Capacity (L.)		Residual Volume Total Lung Capacity (%)	Mixing Index (% N ₂)
			Observed	Predicted			Observed	Predicted	Observed	Predicted	Observed	Predicted		
Patients														
1	39, M	1.86	118	123	81	1.40	3.55	4.03	1.43	1.23	4.89	5.26	29.2	1.34
2	40, M	1.97	92	129	73	0.80	3.60	4.13	1.76	1.26	5.00	5.39	35.3	1.56
3	26, F	1.69	79	100	81	1.20	2.12	3.24
4	62, M	1.99	76	108	65	0.89	2.90	3.66	1.71	1.63	5.17	5.29	33.0	1.06
5	59, M	1.84	86	102	74	1.11	2.85	3.76	1.16	1.67	3.85	5.43	30.2	2.13
6	58, M	1.51	81	85	65	1.06	3.08	3.48	2.04	1.55	5.40	5.03	37.8	1.29
7	29, F	1.66	67	95	83	0.95	2.30	3.06	0.94	0.76	3.25	3.82	28.9	1.09
8	48, M	1.92	133	118	66	0.97	4.43	3.79	2.24	1.16	6.51	4.95	34.4	1.02
9	48, M	1.79	76	110	90	0.95	2.67	3.66	1.54	1.12	4.39	4.77	34.9	0.78
10	39, M	1.83	68	121	80	2.33	0.98	4.03	0.89	1.23	2.03	5.26	43.7	0.96
11	18, M	1.66	132	128	90	1.32	3.39	4.35	0.81	1.09	4.17	5.43	19.5	0.73
12	38, F	1.71	93	92	71	0.93	3.40	3.10	1.23	0.95	4.74	4.04	25.8	0.82
13	36, M	2.05	142	139	84	1.07	4.03	4.25	0.84	1.30	5.01	5.55	16.7	0.63
14	52, M	1.48	116	88	78	1.39	3.37	3.55	2.02	1.58	5.64	5.13	35.8	3.73
15	55, M	1.73	118	100	61	1.08	4.05	3.70	1.95	1.65	5.93	5.35	32.9	1.06
16	33, F	1.60	108	89	72	1.23	2.95	3.02	1.88	0.76	4.21	3.77	28.2	2.35
17	52, M	1.76	119	104	79	1.34	3.22	3.78	1.58	1.68	4.95	5.46	31.8	0.28
18	60, M	1.85	76	101	53	0.80	3.26	3.56	1.47	1.58	4.67	5.14	31.6	1.51
19	44, M	2.00	121	127	78	1.27	2.97	3.98	1.23	1.21	4.46	5.19	27.6	0.53
20	26, M	1.81	74	132	63	0.81	2.90	4.20	2.02	1.05	4.99	5.25	40.4	2.57
21	69, M	1.74	84	88	86	0.83	3.76	3.31	1.93	1.47	5.60	4.78	30.8	1.82
22A	27, M	1.86	145	135	83	1.45	3.23	4.35	0.94	1.09	4.21	5.44	22.4	2.42
22B	27, M	1.86	163	135	81	1.51	3.46	4.35	1.11	1.09	4.57	5.44	24.2	2.57
23	36, F	1.54	94	84	84	1.30	2.50	2.91	1.31	0.89	3.80	3.80	34.5	0.55
24	23, M	1.96	198	145	80	1.26	4.51	4.53	1.18	1.13	5.82	5.66	20.2	0.74
25A	37, F	1.59	77	86	70	1.18	2.22	2.91	2.94	0.89	5.04	3.80	58.4	3.71
25B	38, F	1.65	91	87	76	1.05	2.90	2.90	1.17	0.89	4.27	3.78	27.4	1.36
26	35, M	1.92	101	131	55	1.04	3.20	4.34	1.83	1.32	5.49	5.66	33.4	0.23
27	24, M	1.72	141	128	86	1.64	2.79	4.19	0.73	1.05	3.72	5.23	19.8	0.98
28	16, M	1.22	58	86	88	3.53	0.69	3.63	0.66	0.97	1.34	4.78	49.0	0.77
29	28, F	1.82	81	94	68	1.56	1.77	3.23	1.15	0.81	3.37	4.04	34.2	3.97
30	37, F	1.58	63	85	65	1.17	1.78	2.81	0.63	0.86	2.39	3.66	26.2	2.31
31	40, F	1.54	90	81	73	1.54	1.92	2.67	0.83	0.82	2.71	3.49	30.7	0.50
Mean	39.4	1.75	101.8	107.8	75.2	1.27	2.93	3.65	1.41	1.18	4.43	4.85	31.5	1.48
Standard deviation	± 16.3	± .18	± 19.6	± 19.6	± 9.6	± .50	± .66	± .53	± .54	± .29	± 1.15	± .69	± 8.90	± .99
Normal Subjects														
D. C.	30, M	1.84	155	131	1.03	4.83	4.19	1.04	1.05	5.87	5.23	17.3	1.11
G. G.	27, M	1.83	123	132	75	0.82	4.99	4.43	1.14	1.11	5.79	5.54	19.7	1.54
S. W.	24, M	1.88	134	139	85	0.89	4.78	4.46	1.49	1.11	6.47	5.57	23.0	1.72
A. N.	22, F	1.75	147	107	92	1.10	4.12	3.31	0.84	0.83	4.91	4.14	17.0	0.45
B. F.	25, F	1.75	144	103	80	1.10	4.20	3.30	1.15	0.83	5.16	4.15	22.2	0.43
M. S.	28, F	1.66	143	96	83	1.25	3.73	3.13	1.06	0.78	5.03	3.91	21.0	0.44
E. H.	28, M	1.89	147	136	85	0.92	4.89	4.19	0.76	1.05	6.18	5.24	12.2	0.70
R. H.	24, M	1.93	157	143	89	0.90	5.31	4.31	1.18	1.08	6.16	5.39	19.3	0.93
D. M.	20, M	1.75	4.86	4.32	1.85	1.08	6.71	5.40	27.6	0.59
A. M.	29, M	2.05	253	147	81	1.46	5.40	4.56	1.11	1.14	6.63	5.69	16.7	0.69
J. K.	27, M	1.85	106	134	72	0.73	4.59	4.31	1.29	1.08	6.13	5.38	21.0	0.66
W. A.	33, M	1.96	129	136	83	0.83	4.99	4.35
E. G.	35, M	2.01	187	138	83	1.11	5.20	4.25	1.43	1.30	6.76	5.57	21.2	0.64
Mean	27.1	1.86	152	129	83	1.01	4.76	4.09	1.20	1.04	6.00	5.10	19.9	0.83
Standard deviation	± 4.2	± .11	± 37.5	± 16.7	± 5.7	± .21	± .49	± .49	± .29	± .15	± .50	± .64	± 3.9	± .43

All gas volumes expressed at BTPS.

TABLE III
VENTILATION AND BLOOD GASES, PATIENT AT REST BREATHING AMBIENT AIR

Case No.	O ₂ Uptake (cc./min./M ²)	Ventilation (L./min./M ²)	Ventilation Equivalent (L./100 cc. O ₂)	Alveolar O ₂ Tension (mm. Hg)	Arterial				Respiratory Exchange Ratio
					O ₂ Tension (mm. Hg)	O ₂ Saturation (%)	CO ₂ Tension (mm. Hg)	pH	
Patients									
1	145	4.83	3.32	110	74	93	35	7.40	0.96
2	156	5.02	3.21	121	69	92	26	7.50	0.96
3	102	3.49	3.40	104	93	95	38	7.38	0.79
4	164	7.37	4.49	114	71	92	35	7.42	1.02
5	142	5.35	3.77	109	67	92	36	7.42	0.91
6	177	6.64	3.79	122	92	94	31	7.51	0.97
7	110	4.87	4.44	114	98	97	32	7.41	1.09
8	148	4.40	2.97	92	66	91	39	7.40	0.72
9	159	4.15	2.61	104	85	94	37	7.44	0.76
10	156	6.60	4.25	103	57	88	34	7.45	0.81
11	138	3.45	2.50	97	37	0.67
12	143	3.85	2.69	90	37	7.44	0.87
13	156	5.01	3.23	115	77	93	34	7.42	0.98
14	147	5.67	3.85	111	84	94	33	7.43	0.80
15	177	6.82	3.84	116	76	93	30	7.44	0.99
16	142	3.79	2.67	94	80	94	41	7.37	0.81
17	141	10.70	7.56	92	14	7.52	1.14
18	157	4.54	2.88	92	37	0.92
19	143	7.32	5.12	126	82	95	27	7.44	1.05
20	153	5.05	3.30	112	65	90	28	7.40	0.84
21	116	3.86	3.34	98	79	93	39	7.38	0.85
22A	132	4.88	3.70	98	73	93	41	7.45	0.90
22B	125	5.26	4.21	117	72	92	38	7.42	1.28
23	144	3.90	2.72	104	94	94	32	7.38	0.83
24	168	4.41	2.62	34	0.95
25A	144	6.44	4.47	111	69	93	28	7.36	1.24
25B	130	6.18	4.76	121	95	95	25	7.52	0.84
26	159	5.26	3.31	105	83	94	26	0.83
27	162	4.61	2.85	106	80	94	37	7.39	0.89
28	150	5.05	3.37	103	74	92	45	7.40	1.00
29	160	4.36	2.72	99	69	92	41	7.37	0.80
30	118	3.91	3.32	92	55	87	48	7.39	0.78
31	149	5.27	3.54	109	75	93	37	7.40	0.87
Mean	146	5.22	3.60	108	77	93	34	7.42	0.91
Standard deviation	±24.8	±1.44	±1.00	±9.0	±10.8	±2.1	±6.4	±.04	±.14
Normal Subjects									
D. C.	128	2.64	2.06	48	7.37	0.85
G. G.	153	3.59	2.33	43	7.43	0.82
S. W.	128	2.53	2.00	41	7.37	0.78
A. N.	148	3.30	2.24	102	100	97	40	7.35	0.84
B. F.	142	3.78	2.66	117	105	98	34	7.43	0.87
M. S.	124	2.94	2.38	39	7.39	0.87
E. H.	119	2.39	1.95	39	7.37	0.85
R. H.	144	3.62	2.50	37	7.41	0.86
D. M.	140	3.11	2.22	42	7.39	0.81
A. M.	141	3.07	2.18	105	97	38	7.42	0.95
J. K.	176	5.74	3.26	35	7.45	0.89
W. A.	117	2.83	2.41	94	44	7.35	0.95
E. G.	127	2.55	2.01	101	92	95	42	7.35	0.87
Mean	137	3.24	2.32	106	99	96	40	7.39	0.86
Standard deviation	±60.0	±.86	±.35	±3.8	±.03	±.05

ventilatory function studies which must be considered normal in every respect by any standard of comparison. (Table II.)

Ventilation studies of one of the patients who was examined twice are of interest. A housewife with sarcoidosis was first studied before any treatment (No. 25A). Results suggested obstructive ventilatory insufficiency with a moderate reduction in maximal breathing capacity, a striking increase in residual volume and an abnormally high pulmonary mixing index. (Table II.) Following an intensive course of prednisone (No. 25B) there was marked improvement with an increase of maximal breathing capacity of 14 L./min., a decrease of residual volume from 2.94 to 1.17 L. and a now normal pulmonary mixing index of 1.36 per cent. It was thought that the original obstructive pattern was not on the basis of irreversible obstructive emphysema but rather due to bronchospasm and edema or extrinsic pressure on airways by enlarged nodes, a not unusual pattern in sarcoidosis [20,22].

Ventilation and Blood Gas Studies at Rest: Results for patients and normal volunteers are shown in Table III. Although the mean oxygen consumptions of the two groups varied by no more than 10 cc., marked hyperventilation was the rule among the patients. Their average minute ventilation was 5.22 L., compared to 3.24 L. for the normal subjects and the ventilation equivalent for O_2 , the number of liters ventilated per 100 cc. O_2 taken up, was 3.60 compared to an upper limit of normal for this ratio of 2.50 L./100 cc. [11]. All patients except one (No. 11) were above this limit while only two normal subjects hyperventilated. One of these (B. F.) was subsequently discovered to be in the first trimester of pregnancy when unexplained hyperventilation is a common finding [23]. Other but somewhat less consistent manifestations of hyperventilation in the patient group were a slightly increased respiratory exchange ratio, a reduced arterial P_{CO_2} and an elevated arterial pH. However, the differences were small when compared to the control group and there were individual exceptions. The mechanism of hyperventilation, so characteristic of pulmonary fibrosis and the alveolar-capillary block syndrome, has not been adequately explained. It has been attributed to an overactive respiratory center stimulated by increased stretch reflexes from the lungs. From the teleologic standpoint hyperventilation might be

regarded as an attempt on the part of the organism to increase the oxygen pressure gradient across the abnormal "membrane." However, the mechanism by which this could occur is unknown and hyperventilation usually persists even during 100 per cent O_2 breathing. At any

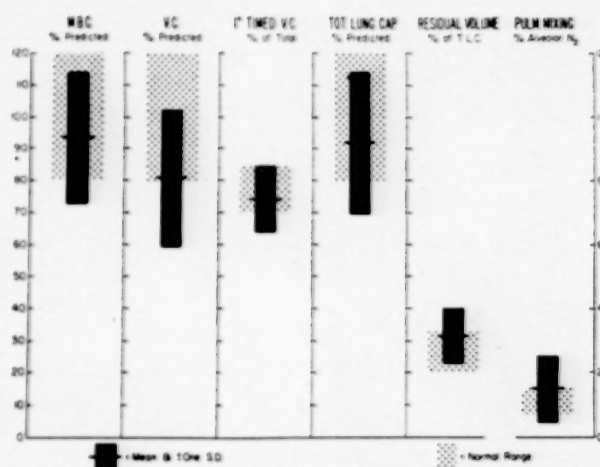


FIG. 2. Results of ventilatory studies in thirty-three patients with "alveolar-capillary block" syndrome. The maximal breathing, vital and total lung capacities are shown as per cent of predicted; the one-second timed capacity as per cent of total vital capacity; the residual volume as per cent of total lung capacity and the intrapulmonary mixing index as per cent "alveolar" nitrogen after seven minutes' oxygen breathing. The mean for each group, together with one standard deviation, are superimposed on stippled areas indicating accepted normal range.

rate, in fifteen of twenty-eight patients hyperventilation did result in a marked elevation of the alveolar P_{O_2} , but only three of these fifteen were able to maintain a normal arterial P_{O_2} , and the mean arterial P_{O_2} of 77 mm. Hg was considerably below the accepted normal of 95 mm. Hg. The arterial O_2 saturation was entirely normal, above 96 per cent, in only five instances. Yet the mean saturation for the group of 93 per cent was only slightly reduced and marked unsaturation was found only twice re-emphasizing that the percentage of saturation does not accurately portray the severity of impairment in O_2 transfer.

Results of Diffusion Studies: These are listed in Table IV and illustrated in Figure 3. The steady state D_{CO} averaged 7.0 cc./min./mm. Hg for the patients compared to 19.5 cc. for the normal control groups. This was the only carbon monoxide method which separated patients from normal volunteers without overlap: the patients' range was 2.5 to 13.1 cc. and the normal sub-

TABLE IV
DIFFUSION MEASUREMENTS, PATIENT AT REST

Case No.	Alveolar-Arterial O ₂ Difference		Direct DO ₂ (cc. O ₂ /min./mm. Hg)	DO ₂ /1.23 (cc. CO/min./mm. Hg)	DCO Steady State (cc./min./mm. Hg)	DCO Single Breath (cc./min./mm. Hg)	Fraction CO Removed (%)	Venous Admixture (%)	Direct DO ₂ (cc./min./mm./M ² BSA)	DCO, Steady State (cc./min./mm./M ² BSA)	DCO, Single Breath (cc./min./mm./M ² BSA)
	Ambient Air (mm. Hg)	Low O ₂ (mm. Hg)									
Patients											
1	36	10	9.2	19.7	36	4.9	10.6
2	52	25	8.0	18.5	35	4.1	9.4
3	11	17	6.7	5.5	5.9	30	4	4.0	3.5
4	43	12	4.2	11.6	16	2.1	5.8
5	42	14	4.7	14.8	23	2.6	8.0
6	30	2	7.6	17.8	23	5.0	11.8
7	16	14	10.9	8.9	6.9	11.0	33	4.2	6.6
8	26	11	11.3	24.4	42	5.9	12.7
9	19	13	13.3	10.8	8.7	13.3	41	8	7.4	4.9	7.4
10	46	40	6.9	5.6	7.0	6.2	22	26	3.8	3.8	3.4
11	8.2	24.2	45	4.9	14.6
12	8.8	18.0	44	5.1	10.5
13	38	23	18.2	14.8	8.4	22.7	35	18	8.9	4.1	11.1
14	27	12	12.1	9.9	8.0	19.6	26	11	8.2	5.4	13.2
15	40	28	8.3	6.7	6.9	17.0	28	20	4.8	4.0	9.8
16	14	11	12.4	10.1	5.7	19.6	33	9	7.8	3.6	12.3
17	3.9	4.7	13	2.2	2.7
18	7.4	21.5	49	4.0	11.6
19	44	23	10.2	8.3	6.6	9.5	24	18	5.1	3.3	4.8
20	47	28	8.7	7.1	6.0	29	30	4.8	3.3
21	19	9	7.5	12.1	33	4.3	7.0
22A	25	27	7.3	5.9	6.5	13.3	31	11	3.9	3.5	7.2
22B	45	27	8.3	6.7	3.9	15.1	21	30	4.5	2.1	8.1
23	10	11	5.8	12.9	38	3.7	8.3
24	13.1	30.6	50	6.7	15.6
25A	42	31	6.5	5.3	5.9	25	25	4.1	3.7
25B	26	22	6.3	5.1	8.8	16.3	35	7	4.0	5.4	9.9
26	22	6	7.8	28.1	33	4.0	14.6
27	26	13	8.8	18.4	18	5.1	10.7
28	29	30	5.1	4.2	2.5	21	15	4.2	2.1
29	30	32	7.4	6.0	6.3	14.9	28	18	4.1	3.5	8.2
30	53	36	6.1	5.0	4.2	19.7	33	28	3.9	2.7	12.5
31	34	29	7.1	5.8	10.6	18	4.6	6.9
Mean	31.9	19.9	9.1	7.4	7.0	16.8	31	17.4	5.3	4.0	9.5
Standard deviation	±12.3	±9.8	±3.3	2.7	±2.1	±5.9	±9.1	±8.3	±1.7	±1.1	±3.2
Normal Subjects											
D. C.	19.1	37.3	64	10.4	20.5
G. G.	16.4	28.9	56	9.0	15.8
S. W.	21.3	34.5	67	11.4	18.4
A. N.	2	17.2	21.5	58	9.8	12.3
B. F.	12	19.0	24.4	62	10.9	14.0
M. S.	21.5	25.7	65	13.0	15.8
E. H.	16.8	31.0	72	8.9	16.2
R. H.	26.8	32.6	68	13.8	16.9
D. M.	18.5	29.3	60	10.6	16.7
A. M.	8	0	24.7	34.4	68	12.0	16.8
J. K.	17.2	32.4	42	9.3	17.5
W. A.	19.7	61	10.0
E. G.	9	15.6	30.4	63	7.8	16.8
Mean	8	19.5	30.2	62	10.5	16.5
Standard deviation	±3.2	±4.6	±7.5	±1.7	±2.0

All gas volumes expressed at STPD.

jects 15.6 to 26.8 cc. The steady state D_{CO} was also calculated in terms of body surface (Table iv) although the number of our normal subjects was too small to demonstrate the pertinence of this calculation.

The single breath D_{CO} , obtained in twenty-nine patients, averaged 16.8 cc./min./mm. Hg compared to 30.2 cc. for the normal group. Six patients had results which fell within the normal range of 21.5 to 37.3 cc. In the patient group the diffusion capacity determined by this method was 140 per cent larger than the average by the steady state method and for the normal control group it was 55 per cent larger.

The fraction CO removed (F_{CO}), calculated from data available from the steady state D_{CO} determination, provided a good separation between the two groups, with an average value of 31 per cent for the patients and 62 per cent for the normal subjects. There was only one normal subject (J. K.) below and one patient (No. 24) above the accepted dividing line [77] of 50 per cent. This was surprising because the F_{CO} removed has been described as only a relatively crude index of diffusion capacity. Additional facets of this measurement will be discussed.

The directly determined D_{O_2} could be calculated in only eighteen patients, although alveolar-arterial P_{O_2} differences (A-a gradients) were measured at two levels of O_2 breathing in twenty-eight subjects. (Table iv.) Most of the failures were due to improper selection of the "low" O_2 concentration of the inspired gas for the second measurement. If the concentration was too high the O_2 saturation was still in the flat portion of the dissociation curve and the assumption of a minimal "venous admixture" effect was not valid. If the concentration was too low the saturation was depressed below 75 per cent on the steep portion of the curve, so that the assumption of an unchanged cardiac output, arteriovenous O_2 difference, and diffusion could no longer be made. In some instances, the O_2 consumption during the two determinations differed by more than the acceptable limit, and on a few occasions, the arterial P_{O_2} determinations were thought unreliable because of failure of multiple analyses to check within 2 mm.

The D_{O_2} was less than the minimum normal of 15 cc./min./mm. Hg in all but one case (No. 13). When the D_{O_2} was calculated in terms of D_{CO} there was remarkable agreement between the two steady state methods: the mean for the $D_{O_2}/1.23$ was 7.4 ± 2.7 cc./min./mm. Hg

and the mean for D_{CO} was 7.0 ± 2.1 . (Table iv.) It is of interest that, in spite of our strict criteria for selection of patients, "pure" diffusion defects were rare: the calculated venous admixture was greater than the upper limit of normal of 6 per cent in all patients but one (No. 3). An abnormal

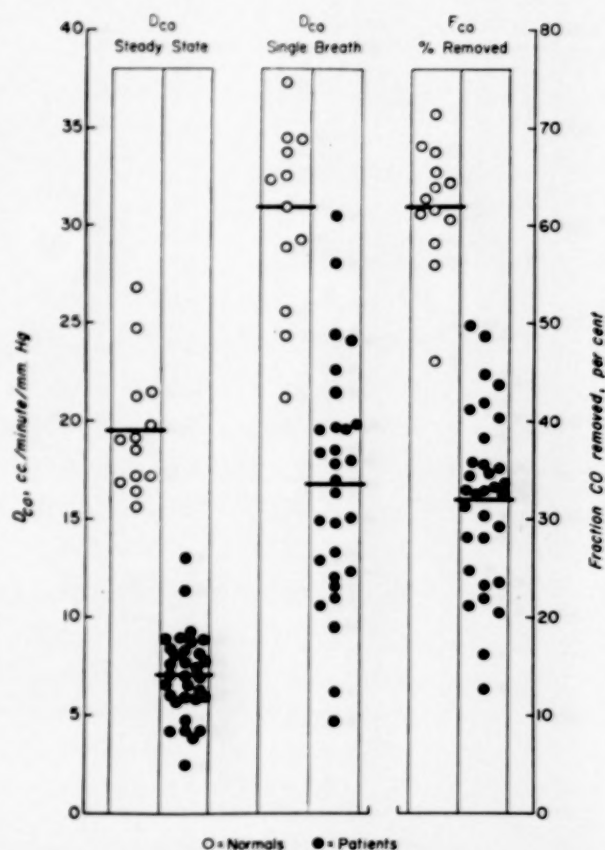


FIG. 3. Mean and individual values for carbon monoxide diffusion capacities (D_{CO}) in cc./min./mm. Hg by the steady state and single breath techniques and the fraction of carbon monoxide removed (F_{CO}), as per cent, all obtained with subjects at rest, are shown for thirteen normal volunteers and for thirty-three patients with "alveolar-capillary block" syndrome.

ventilation-perfusion relationship has been described in some advanced cases with alveolar-capillary block syndrome [19] but the almost invariable and considerable degree of venous admixture in this group with relatively early disease was not anticipated.

The limitation of the room air A-a gradient for definition of oxygen transfer defects has been mentioned. Yet, among twenty-eight patients in this group there was only one with an almost normal gradient (No. 23) and only one with an elevated room air gradient but a normal D_{O_2} (No. 13). From the clinical standpoint it appears

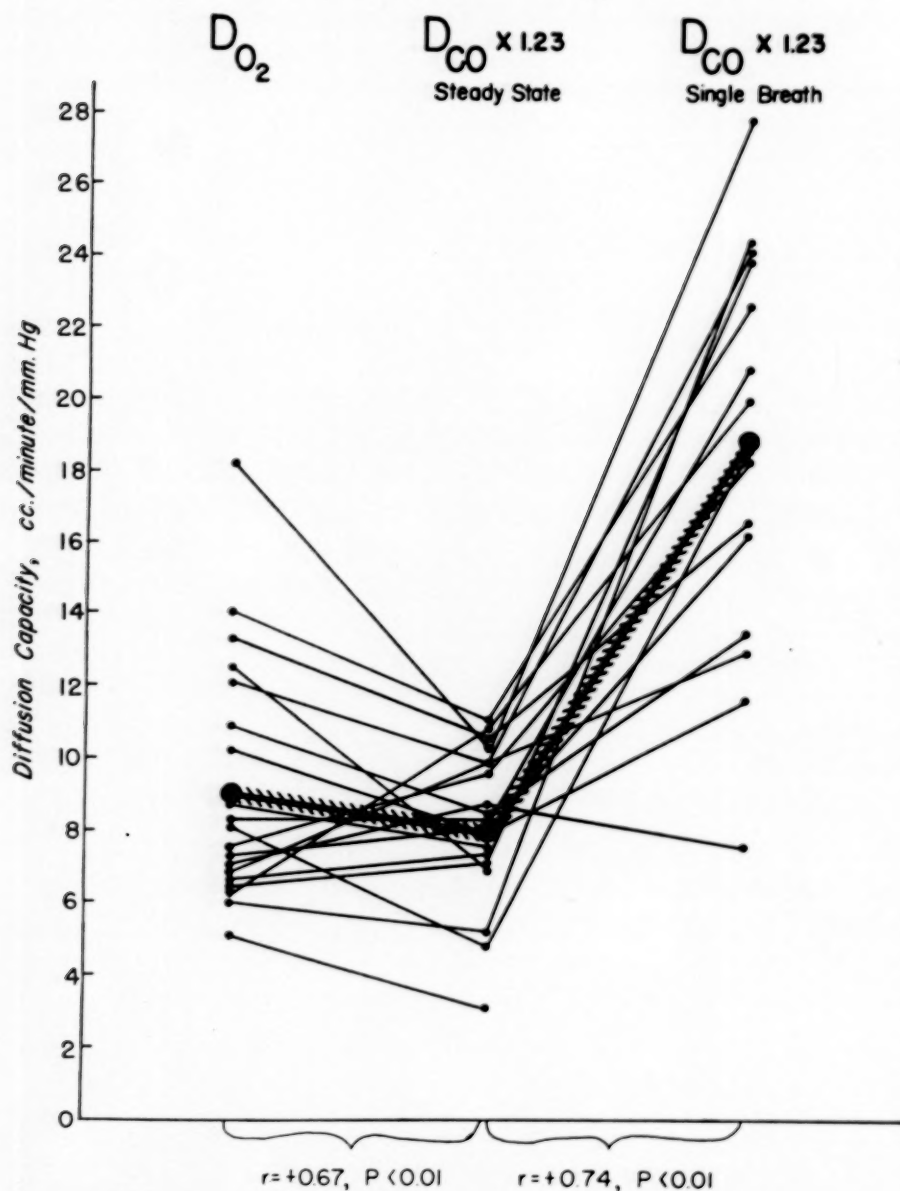


FIG. 4. Comparison of directly determined oxygen diffusion capacity (D_{O_2}) with carbon monoxide diffusion capacities (D_{CO}) obtained by the steady state and single breath techniques in eighteen patients with "alveolar-capillary block" syndrome. The CO values were multiplied by 1.23 to account for the slightly greater diffusibility of O_2 . Results for individual patients and means for the group are indicated. All studies were performed at rest.

that, because of the almost constant association of diffusion defects with abnormally large venous admixture, the room air A-a gradient alone is a significant measurement in patients in whom diffusion impairment is suspected. The importance of the room air A-a gradient in this regard has been emphasized by Wright [20].

Results of the three diffusion capacity measurements in the same patients are compared in Figure 4. Individual values for the two CO methods were multiplied by the constant 1.23 to

correct for the greater diffusibility of oxygen [10]. The directly determined D_{O_2} of 9.1 cc. in this group compared very well with the mean corrected steady state D_{CO} of 7.9 cc. with a coefficient of correlation of +0.67 ($P < 0.01$) for individual patients. The mean single breath D_{CO} , similarly corrected, was 18.4 cc. or more than twice as large as the means for the other two methods. However, there was also a highly significant correlation between the two D_{CO} methods ($r = +0.74$, $P < 0.01$). Possible rea-

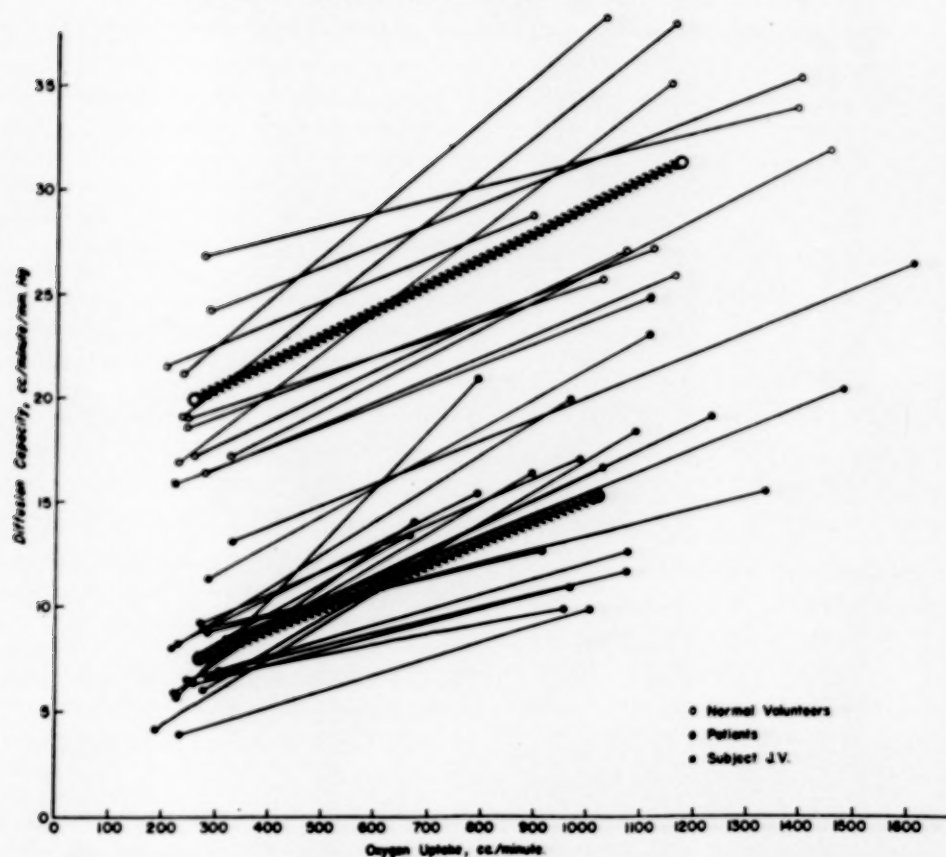


FIG. 5. The steady state carbon monoxide diffusion capacities (D_{CO}) at rest and during moderate exercise (1.5 to 3 m.p.h., 8 per cent grade) in eleven normal subjects and eighteen patients with "alveolar-capillary block" syndrome. The severity of the exercise is indicated in terms of O_2 uptake per minute.

sons for the higher values with the single breath method will be discussed.

Exercise studies could not be carried out in all patients because some were too ill, others had active tuberculosis and two were crippled by skeletal malformations. The steady state D_{CO} method was the only one for which comparison between rest and exercise was possible. It was not feasible in these outpatients to maintain arterial cannulization long enough for a second two-level A-a gradient determination, and the single breath method was not applicable because of the difficulty in holding breath during activity. Results of the steady state D_{CO} method during exercise have been reported in detail previously [8,24].

Comparison between rest and exercise was possible in twenty patients and in eleven normal subjects. (Fig. 5.) The severity of exercise was expressed in terms of minute O_2 uptake. The measurements for the normal subjects do not represent the so-called "maximal diffusion capacity" since no attempt was made to produce

maximal stress. Rather, the exercise of the control subjects was limited to the degree which was tolerable to most patients [24]. It is evident from Figure 5 that (1) for the same intensity of activity the relative increase in D_{CO} was about the same for patients and for normals, and (2) the degree of discrimination of the test was equally good under either condition. Both conclusions are contrary to observations of Bates *et al.* [25] in six patients with pulmonary emphysema they found no increase from resting D_{CO} values while walking on the level at two to three miles per hour. Their data are not strictly comparable because the severity of the exercise was expressed differently; the steady state condition was not remarked upon; the patients had severe emphysema; and end-tidal CO analyses [26] rather than arterial CO_2 tensions were used for calculation of the alveolar CO concentration.

Comparison of D_{CO} studies with results of others. Reports, to date, of clinical application of the two D_{CO} methods are limited to five patients

with vaguely defined pulmonary disease [27]. All had complicating pulmonary emphysema and only two were studied at rest. Comparison is therefore not possible but in one of the two patients the steady state D_{CO} was 15 per cent smaller than the single breath value and in the other patient it was four to five times larger.

For normal subjects at rest the data of Filley *et al.* [8] are available for comparison of the steady state D_{CO} method. Their mean D_{CO} for seven individuals studied on twelve occasions was 17.9 cc./min./mm. Hg and compared well with our mean of 19.5 cc. (Table iv.) However, their range of 10.5 to 28.0 was greater than ours and four of their subjects had a D_{CO} which would fall in our patient range. This may have been, in part, because patients with arrested minimal tuberculosis were included among their normal subjects, because their method of CO gas analysis was different from ours, and also because all but two of their subjects hyperventilated; their ventilation equivalent for O_2 was more than 2.5 L./100 cc. and the mean value for the group (where O_2 uptake was indicated) was 3.00 compared to our 2.32 L./100 cc. (Table iii.) As a corollary, their F_{CO} , calculated in the same manner as ours, averaged only 53 per cent compared to our mean of 62 per cent. (Table iv.)

Also of interest in this connection is a comparison of the two D_{CO} methods in six normal subjects just published by Bates and Pearce [28]. The steady state D_{CO} in the supine position, calculated from end-tidal samples [26] rather than the Bohr equation, averaged 18.1 cc./min./mm. Hg, almost identical with our mean. However, the single breath D_{CO} in the sitting position was only 16.8 cc. compared to our 30.2 cc. The cause for this marked discrepancy with use of an identical method is not immediately apparent. In the same subjects they found that the D_{CO} is about 3 cc. greater by either method with the subject lying flat than in the sitting position. If confirmed, this would mean that our large discrepancy between the two methods would have been even larger if the same position had been used for both.

CASE REPORTS

Detailed discussion of the clinical material comprising this study is not intended and correlation of symptoms and signs to laboratory findings is limited to presentation of Tables I to IV. Although emphasis has been placed on comparison of methods, presentation of a typical

case may serve to bring the entire group of patients into proper perspective and may illustrate both the indications for, and the significance of diffusion studies in this group.

Patient E. P. (No. 22), a twenty-seven year old dairy farmer, was referred from the Boston Veterans Administration Hospital for study in August 1955 because of progressive dyspnea, cough, chest pain and weight loss. The present illness began three years before when an erythematous, papillar eruption developed over the patient's lower extremities. A roentgenogram of the chest at that time revealed fine nodular infiltration in the right upper lobe. This progressed to involve both lungs during his hospital stay. The only other finding of interest at that time was a positive reaction to first strength tuberculin.

The patient was readmitted three years later because of a right spontaneous pneumothorax. During the interval he had noted increasing exertional dyspnea, non-productive cough, bilateral chest pain and moderate weight loss. The lung re-expanded promptly and a scalene node biopsy was performed, but only normal nodes were found.

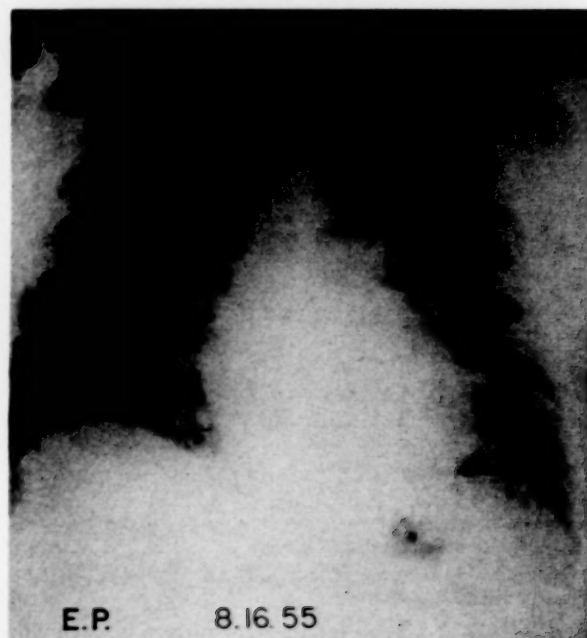
He was readmitted for the third time six months later because of progressive symptoms with disabling dyspnea and increasing pulmonary infiltration. (Fig. 6A.) After all other diagnostic procedures were exhausted a lung biopsy was performed and the histologic diagnosis was eosinophilic granuloma. (Fig. 6B.) He was given cortisone for eight weeks but there was no clinical improvement or roentgenographic changes. Pulmonary function studies were then requested prior to a trial of radiation therapy. The results of these studies are summarized in Table v. Ventilatory studies revealed normal breathing dynamics and a 25 per cent uniform reduction of all lung volume compartments. Blood gas studies showed minimal O_2 unsaturation, marked diminution of O_2 tension and a moderate increase of the A-a gradient both during ambient air and low oxygen breathing. At rest, the directly determined D_{O_2} , the D_{CO} by both methods, and the F_{CO} were all about one-third of normal and there was marked hyperventilation. During exercise the steady state D_{CO} and the F_{CO} were again reduced to one-third of normal and he ventilated almost twice as much as a normal individual at the same rate of activity. It was concluded that the severe respiratory complaints in the absence of a measurable defect in the mechanics of breathing were adequately explained by the demonstration of a severe degree of alveolar-capillary block.

During the next two months the patient received radiation totaling 3,200 r to both lungs. There was no interruption in the progressive course of the illness and he was referred four months after the initial studies for objective evaluation of the results of radiation treatment. Results of this second series of tests revealed changes of a magnitude which were all well within the

limit of error of the particular technic. (Table v.) The only exception was a further increase in the A-a gradient during ambient air breathing and consequently a marked increase from 11 to 30 per cent in the calculated venous admixture. It was concluded that radiation therapy had not resulted in any change of the degree of alveolar-capillary block and, on the basis of a single observation, it was suggested that possibly the dead space-like ventilation and venous admixture-like perfusion were increased.

The selection of our patients, as indicated initially, was made on the basis of roentgenographic evidence of finely dispersed parenchymal lesions, normal ventilatory function or dyspnea out of proportion to the measured ventilatory defect, and impairment of diffusion capacity. It is of interest that patients who were seen at our laboratory with x-ray findings as described almost invariably also had demonstrable impairment of diffusion capacity. Deserving emphasis are patients who fulfilled all the criteria except that they had normal diffusion capacities. During the past two years two individuals were seen who had diffuse miliary involvement by roentgenogram but, unexpectedly, normal oxygen and carbon monoxide diffusion measurements. In one such individual, not included in this report, certain abnormal findings including increased alveolar and arterial O_2 tensions and respiratory quotient, and decreased arterial CO_2 tension and F_{CO} could all be explained on the basis of voluntary hyperventilation during the examinations. In the other patient the results of all studies were entirely normal despite a strikingly abnormal roentgenogram of the chest. This individual (Subject J. V.) was not included among the patients or normal subjects of this report but is of sufficient interest to merit presentation.

Subject J. V., a twenty-one year old white Marine, was referred from the U. S. Naval Hospital, Chelsea, Massachusetts because of unexplained diffuse pulmonary infiltration. The patient was a vigorous athlete without symptoms. A normal roentgenogram of the chest was obtained one year before admission. Four months later, following a tonsillectomy, a mild cough led to another roentgenogram of the chest which revealed diffuse, mottled miliary infiltration. (Fig. 7.) Further films revealed no change during the next six months. Past and family histories were non-contributory except that he had worked with steel on a drill press for six months many years ago. Physical examination was entirely within normal limits. Routine laboratory examinations and skin tests for blastomycosis



6A

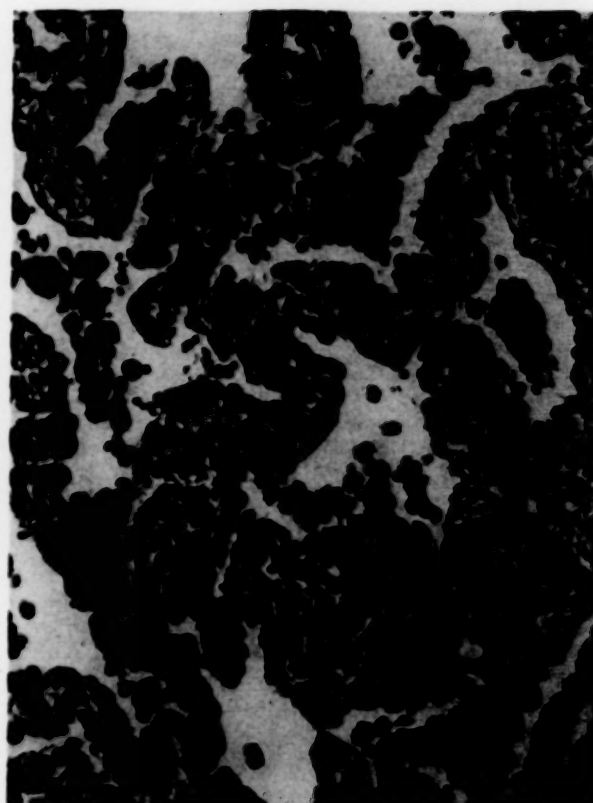


FIG. 6. A typical patient with "alveolar-capillary block" syndrome included in this study. A, Case 22A. A chest roentgenogram of patient E. P., a twenty-seven year old dairy farmer. There is a widely dispersed granular infiltration of both lungs. B, Same case. A biopsy specimen of the lung. The final diagnosis was eosinophilic granuloma.

TABLE V
CASE REPORTS

Test	Patient No. 22, Radiation Treatment			Subject J. V.	
	Before	After	Predicted Normal	Determined	Predicted Normal
Ventilation:					
Maximal breathing capacity, L./min.	145	163	135	186	136
Vital capacity, L.	3.23	3.46	4.35	4.52	4.46
One-second vital capacity, % of total vital capacity	83	81	>75	80	>75
Pulmonary mixing index, % nitrogen	2.42	2.57	<1.5	0.63	<1.5
Lung Volumes:					
Residual volume, L.	0.94	1.11	1.09	1.31	1.12
Total lung capacity, L.	4.21	4.57	5.44	6.19	5.58
Residual volume/total lung capacity $\times 100$, %	22.4	24.2	20	21.1	20
Arterial Blood Gases:					
Oxygen saturation, %	93.2	92.8	96	96.5	96
Oxygen tension, mm. Hg.	73	72	90–100	91	90–100
Carbon dioxide tension, mm. Hg.	41	38	45	45	45
Alveolar-arterial O ₂ tension difference, mm. Hg, breathing room air	25	45	<10	2	<10
Alveolar-arterial O ₂ tension difference, mm. Hg, breathing low O ₂ mixture	27	27	<10	6	<10
pH	7.45	7.42	7.34
Diffusion Studies:					
DO ₂ , steady state, cc./min./mm. Hg.	7.3	8.3	>15	Not calculated	>15
Dco, steady state, cc./min./mm./Hg.	6.5	3.9	19 \pm 3	15.9	19 \pm 3
Dco, single breath, cc./min./mm. Hg.	13.3	15.1	30 \pm 5	26.8	30 \pm 5
Fraction CO removed, %	19	24	>50	57	>50
Venous admixture, % of cardiac output	11	30	<6	Not calculated	<6
Oxygen uptake, cc./min.	246	233	222
Ventilation equivalent for O ₂ , L./100 cc.	3.70	4.21	<2.5	2.28	<2.5
Diffusion Studies, Exercise (3.6 mph, 8%):					
Dco, steady state, cc./min./mm. Hg.	12.6	9.8	31 \pm 5	24.8	31 \pm 5
Fraction CO removed, %	17	16	35	38	35
Oxygen uptake, cc./min.	1075	1006	1119
Ventilation equivalent for O ₂ , L./100 cc.	3.98	3.60	2.5	2.30	2.5

sis, coccidiomycosis and histoplasmosis were negative. The tuberculin test was negative in both strengths.

Pulmonary function studies are summarized in Table v. Ventilation, arterial blood gases and Dco both at rest and during exercise (Fig. 5) were all within the normal range. This was also the only patient with diffuse pulmonary involvement who had normal A-A gradients during both room air and low oxygen breathing. The DO₂ could therefore not be calculated. The clinical diagnosis was pulmonary fibrosis or granulomatosis of unknown etiology. A supra-clavicular node biopsy specimen showed only chronic inflammation and lung biopsy was not obtained.

COMMENTS

Discussion of the alveolar-capillary block syndrome is not within the scope of this paper.

Several reviews of the clinical and physiologic manifestations of this condition are available [19,24,29]. The main purpose of this study was to evaluate and compare the carbon monoxide technics in regard to estimation of diffusion capacity. The decision to restrict this study as much as possible to patients with uncomplicated alveolar-capillary block syndrome deserves comment because impaired diffusion must be part of the physiopathologic picture in other pulmonary disease entities. Sheppard *et al.* [30], discussing the so-called "maximal diffusion capacity" in patients with emphysema, suggested that impairment in the ability to transfer oxygen exists in this disease. Kjerulf-Jensen and Kruhøffer [31], measuring gas exchange with radioactive carbon

monoxide and Bates *et al.* [25] both found reduction in the D_{CO} up to 50 per cent in severe pulmonary emphysema. However, it has been pointed out by Forster *et al.* [32] and others that, if there is disproportion between alveolar ventilation and pulmonary diffusion capacity in various parts of the lung the steady state technics may not be accurate. Since the interpretation of diffusion data in the presence of complicating emphysema is still controversial, it appeared warranted to exclude patients with known distribution and obstructive defects from this study. Further, it was hoped that selection of patients with "pure" diffusion difficulties would permit study of the effects of hyperventilation on blood gas tensions in the absence of excessive venous admixture. From the clinical standpoint, the quantitation of the diffusion defect in severe emphysema is of little importance because measurements of mechanical disturbances and attending ventilatory insufficiency correlate well with respiratory symptoms.

Concerning methodology, the results by each of the three technics for estimation of diffusion capacity should be the same if the patients selected would have only a diffusion abnormality and if the measurements were technically perfect. That this was not true is apparent from Table iv and Figure 4. Consideration of the technical errors [8,15,33] and clinical and theoretic limitations [6,27,32] of each method might clarify some of the discrepancies.

From the technical standpoint of ease of performance, the *single breath D_{CO} method* might be considered first. When the residual volume is known, this test requires only a few minutes and blood gas analyses are not needed. The alveolar sample is analyzed for CO and He by rapid physical methods. The infra-red CO meter in our hands has proved to be a most stable and satisfactory instrument. The He katharometer requires more care and the presence of CO₂ in the gas must be corrected for, but, with frequent checks, reproducible results are usually obtained. The actual D_{CO} values obtained by us with this method are in agreement with those of Forster *et al.* [9,27] and, in spite of the higher absolute figures, correlate well with the steady state D_{CO} .

Several clinical difficulties were encountered. The forced expiration followed by a rapid, maximal inspiration with breath holding for ten seconds requires some training. Accurate timing of the period of breath holding is important because the D_{CO} is expressed in cc. per minute

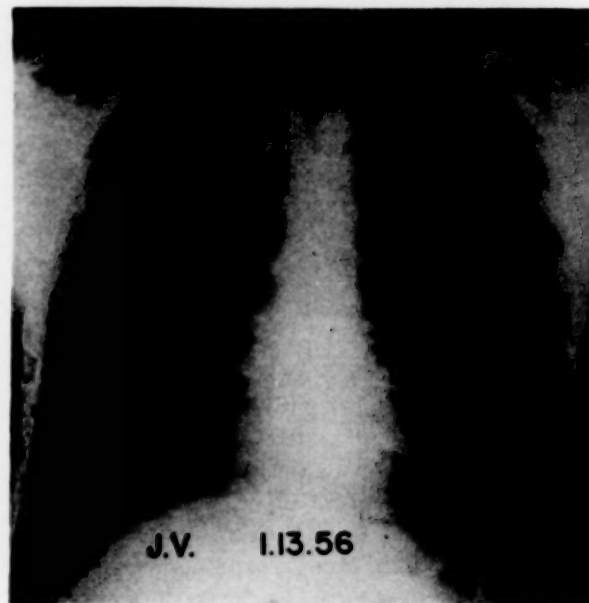


FIG. 7. Chest roentgenogram of subject J. V., a twenty-one year old Marine. This individual, whose functional data are shown in Table v, was not included in this study because all diffusion data were entirely within the normal range in spite of diffuse pulmonary involvement by roentgenogram.

and thus a factor of 6 is involved; correction is difficult because the D_{CO} decreases with increasing time of breath holding [9]. Timing starts with the beginning of inspiration, therefore the speed with which this effort is made must be considered [28]. We have attempted to minimize these errors by requiring duplicate determinations to check within 10 per cent. Although all patients in this group could hold their breath for ten seconds at rest, only a few could perform this maneuver during exercise. Comparison of this method with the others was therefore limited to resting conditions where the steady state technics are least accurate. Another practical limitation of the single breath method is the need for a considerable gas sample. To obtain effective "alveolar" air at least 700 cc. are required to flush the dead space of the subject and apparatus plus another 400 cc. for the physical gas analyses. Obviously, patients with severe "restrictive" ventilatory insufficiency and vital capacities below 1,100 cc. could not be examined by this technic. Of two patients with very low vital capacities in our series, one (No. 28) could not be studied by this method and the other (No. 10) was the only one in whom the single breath D_{CO} was lower than the steady state D_{CO} , raising the question of the validity of the alveolar sampling in this instance.

From the theoretic standpoint there are several possibilities why the results by this method are consistently higher than for the steady state technics. Our findings agree with Forster *et al.* [9] in that the single breath D_{CO} decreases with increasing length of breath holding. This has been explained by postulating a number of "diffusion phases" for the lungs. We think it possible that the technic as described samples only the fastest ventilated and most rapidly perfused areas and thereby leads to a considerably higher diffusion capacity than that of the mean of the lungs. This effect should be more prominent in patients with pulmonary disease where there is considerable local variation in the effectiveness of ventilation and perfusion and should be less prominent in normal subjects in whom local performance is more nearly equal to mean performance. This was borne out by our clinical experience: in patients the average breath holding D_{CO} was 140 per cent larger than the steady state D_{CO} whereas in normal subjects it was only 55 per cent larger. Another factor might be that the lung volume at which diffusion occurs is maximal with the single breath while it is considerably lower, or approximately functional residual volume plus one-half tidal volume, in the steady state methods. It would appear plausible that the increased total alveolar volume would result in a greater interface for diffusion. Although Forster [34] has found no more than a 15 per cent variation in D_{CO} with breath holding at different lung volumes we have observed differences of as much as 50 per cent. In the same normal subjects the single breath D_{CO} decreases rapidly with less than maximal inspirations and approaches the steady state D_{CO} value with breath holding in the pulmonary resting position [35]. Additional study is needed to clarify this point. Other theoretic considerations of CO uptake have been reviewed in detail [7,9,32].

The steady state D_{CO} method occupies an intermediate position with regard to ease of performance and opportunity for technical error. The only required arterial blood analysis is for carbon dioxide tension. However, an error of 2 mm. in this determination may lead to an error of as much as 20 per cent in the calculated D_{CO} [8], and the direct bubble method for this measurement is tedious and technically difficult. Fortunately, there are a number of checks which help maintain a reasonable degree of accuracy in this regard. The directly determined CO_2 tension

can be compared with that calculated from the arterial pH and CO_2 content. In addition, the physiologic dead space can be calculated from the Bohr equation using the arterial and expired CO_2 tensions. The credibility of the dead space value reflects the accuracy of the tension determination. This check is best with large tidal volumes during exercise when small changes in CO_2 tension cause relatively large changes in the calculated dead space [15]. The D_{CO} is affected not only by errors in analysis of arterial CO_2 tension but also by errors in determination of the expired CO concentration. Accuracy here is more critical than with breath holding because the concentrations of CO to be measured are only one-third to one-fifth as large. The less CO is removed from the inspired gas the more accurate the analysis; therefore, errors are likely to be smaller in patients than in normal subjects and smaller during exercise than at rest. If a 2 per cent error in expired CO analysis happens to coincide with an error in the opposite direction of 2 mm. in the CO_2 tension analysis the resting D_{CO} in normal subjects may be 40 per cent in error [8].

The major theoretic objections to this method deal with its two basic assumptions: (1) absence of an alveolar-arterial pressure gradient for CO_2 and (2) absence of a significant plasma CO tension. There is general agreement that the arterial and the mean alveolar CO_2 tensions are not appreciably different in normal subjects [5,7,33,36]. Venous admixture in normal amounts should cause no measurable change of CO_2 tension from the pulmonary capillaries to the peripheral arteries. The diffusibility of CO_2 , which is twenty-one times greater than that of O_2 , would make the normal gradient so small as to be immeasurable with present technics. It has been suggested, however, that the CO_2 equilibration of end-capillary blood and alveolar gas may not be as complete in patients with diffuse pulmonary disease [33].

The validity of the assumption that the pulmonary capillary CO tension ("back pressure") is negligible [7,10] has been questioned [8,9,32,37]. According to equation (1) a neglected back pressure of significant magnitude would result in an underestimation of the D_{CO} . One cause for a pulmonary capillary CO tension is the slowness of the reaction of CO with the intracellular hemoglobin which permits accumulation of CO in plasma [37]. This should affect the results of the two D_{CO} methods proportionally. Another

reason for a significant capillary CO tension may be a sufficiently large carbon monoxide hemoglobin (COHb) saturation to result in a measurable blood CO tension in equilibration with it. From the nomograms of Forbes *et al.* [38] the average increase in COHb, breathing 0.1 per cent CO for the period used in this procedure, would be about 2.4 per cent and from the data of Pace *et al.* [39] this estimate would be 1.1 per cent. The latter authors estimate that COHb saturation in smokers is between 2 and 3 per cent. Accordingly, the total COHb saturation should be no more than 5 per cent at the end of the determination. The back pressure from such low concentrations of COHb should not produce a significant error in the results. From the clinical standpoint we have not been able to detect any significant difference in the determined D_{CO} in smoking and non-smoking normal subjects nor have resting studies repeated at thirty minute intervals in normal subjects shown any progressive decrease in D_{CO} . However, we have been able to demonstrate a considerable difference of initial COHb saturation between smokers and non-smokers. Also, from the seventh through the ninth minute of 0.1 per cent CO breathing we have found up to 8 per cent COHb saturations and much higher values during exercise. Furthermore, there has been no appreciable decrease of COHb saturation over the course of the next thirty minutes [35]. More detailed investigations of the magnitude of back pressure are being carried out currently.

Clinically, the most important limitation of the steady state method is the required arterial cannulization. Possible means of circumventing this have been discussed [24,26].

The *fraction CO removed* (F_{CO}) has been considered an index of the effectiveness of diffusion [11]. Bates [11] found that young normal subjects at rest take up between 41 and 62 per cent of the carbon monoxide presented to the lungs and that this F_{CO} decreases with increasing minute ventilation during exercise and, even more, during voluntary hyperventilation. We have calculated the F_{CO} for the subjects comprising this study to ascertain its clinical usefulness in relation to the more complex procedures. The calculation was modified by using alveolar ventilation rather than total minute ventilation [8] because the physiologic dead space was known to us. In Figure 8 this modified F_{CO} was compared to the steady state D_{CO} to demonstrate the very significant correlation between these

two tests ($r = -0.75$, $P < 0.01$) in patients and normal subjects. The only normal subject who had an F_{CO} of less than 50 per cent (Table IV), and fell within the patient range (Fig. 3), was J. K. He was also the only normal subject who hyperventilated at rest, with a nearly doubled minute

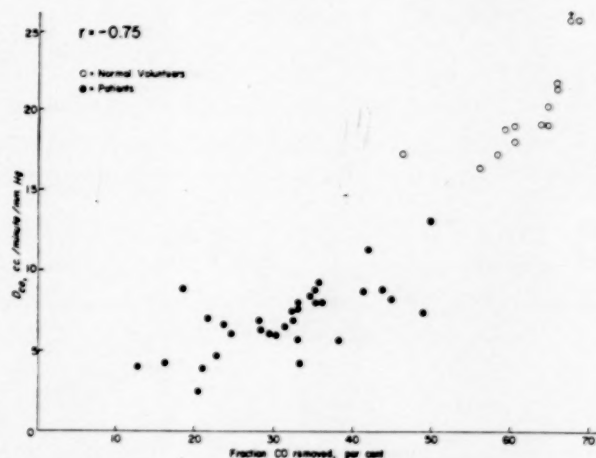


FIG. 8. The steady state carbon monoxide diffusion capacity (D_{CO}) plotted against the fraction of carbon monoxide removed (F_{CO}) for fifteen normal subjects and for thirty-three patients with "alveolar-capillary block" syndrome, all obtained with the subjects at rest. There was a good correlation ($r = -0.75$, $P < 0.01$).

ventilation and a ventilation equivalent for O_2 of 3.26 L./100 cc. (Table III.) Since hyperventilation results in a lowering of the F_{CO} , and since patients with alveolar-capillary block syndrome characteristically hyperventilate, it was thought possible that the F_{CO} values obtained in this group may have been merely a reflection of the hyperventilation rather than the degree of impaired diffusion. In Figure 9 the F_{CO} was plotted against the "efficiency" of ventilation expressed in terms of the ventilation equivalent for O_2 . The F_{CO} correlated equally well with the ventilation equivalent ($r = -0.71$, $P < 0.01$) and with the steady state D_{CO} and therefore may be equally well a function of hyperventilation. Therefore, in patients with alveolar-capillary block the correlation between F_{CO} and D_{CO} is likely to be good. In subjects who hyperventilate voluntarily and in patients who hypoventilate because of ventilatory insufficiency but who also have diffusion difficulties the correlation may be expected to be poor.

The *direct determination of the D_{O_2}* is fraught with more technical difficulties than any of the CO methods. Although we have had considerable experience with this method during the past five

years, we were able to measure the two-level A-a gradients in only twenty-eight of the thirty-three studies in this series and in only eighteen could the D_{O_2} be calculated. This method depends on the accuracy of the arterial O_2 tension determination, the most exacting of the blood

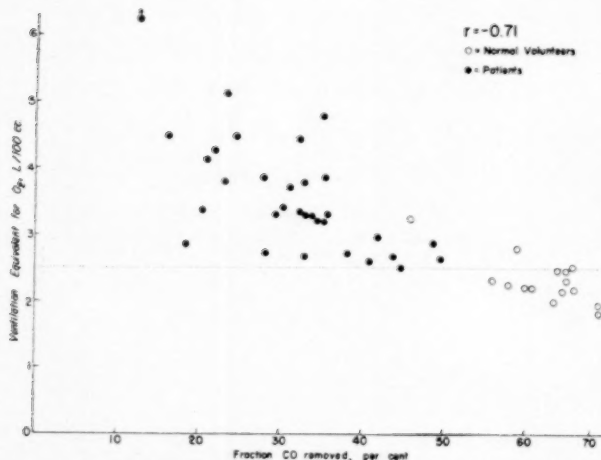


FIG. 9. The ventilation equivalent for O_2 in liters/100 cc. plotted against the fraction of carbon monoxide removed (F_{CO}), in per cent, for fifteen normal subjects and for thirty-three patients with "alveolar-capillary block" syndrome, all at rest. There was a good correlation ($r = -0.71$, $P < 0.01$). The upper limit of normal for the ventilation equivalent of 2.5 L./100 cc. is indicated by the dotted horizontal line.

gas analyses. Unlike the previously mentioned checks on the accuracy of the CO_2 tension, there is no means of checking the O_2 tension except by multiple analyses. During room air breathing the saturation falls on the flat portion of the O_2 dissociation curve and knowledge of O_2 saturation and pH is of no help. The technical difficulties are doubled because of the repetition at the low O_2 level and also cause a delay before the second examination. It is likely that eventually polarographic methods for O_2 tension analysis [4,40] will greatly facilitate this measurement but in our hands the polarograph has never equalled the accuracy of the bubble technic.

Clinical application of the procedure is difficult because of the necessary prolonged arterial cannulization and because low oxygen breathing may be contraindicated in certain conditions. The simultaneously obtained estimate of the percentage of venous admixture is an advantage of this method (Case Nos. 22A and 22B, Table v) not shared by the CO technics.

From the theoretic standpoint, the validity of the assumption that there is no CO_2 gradient is as important here as in the steady state D_{CO}

method since the arterial alveolar CO_2 tension is required for the calculation of the mean alveolar O_2 tension. In addition, the use of the Bohr integration procedure has been criticized on the basis that this calculation is applicable only if the thickness of the membrane is the same along the length of all the capillaries [37]. Another basic assumption is that the diffusion capacity is not altered by low O_2 breathing. Yet Cander and Forster [41], with the single breath D_{CO} method, have found a pronounced increase of diffusion capacity by lowering the O_2 concentration within the lungs. This was thought to reflect a change in the hemoglobin affinity for carbon monoxide. Bartels *et al.* [40] found average D_{O_2} values of 17.0 cc./min./mm. Hg with room air breathing and of 24.2 cc. during hypoxia. The degree of hypoxia was not stated and, because an increase in cardiac output was noted, the results are not strictly comparable to those published by Donald *et al.* [17].

The clinical diagnosis of alveolar-capillary block syndrome can be made with considerable certainty merely on the basis of an x-ray finding of diffuse, finely dispersed pulmonary parenchymal lesions, regardless of etiology. Quantitative measure of the pulmonary diffusion capacity confirmed the diagnosis in forty-four of forty-six patients (96 per cent) in this and another series [24] who had roentgenographic findings as described. Considerable impairment of diffusion could be demonstrated in the absence of any subjective symptoms (Case Nos. 24 and 27) and dyspnea was not the chief complaint in 23 per cent of all patients. (Table I.) Laboratory measurements of breathing capacities and lung volumes were of no help in confirming the diagnosis because they ranged all the way from normal to markedly abnormal (Table II) and the degree of restrictive ventilatory insufficiency, if any, was not particularly related to the severity of the diffusion defect. This is an important consideration for disability evaluation of patients with respiratory complaints. Most conventional measurements of arterial blood were equally unrewarding. The arterial O_2 saturation was often normal both at rest and during exercise [24] and even the arterial O_2 tension at times could be maintained within normal limits by increased alveolar ventilation. (Table III.) Invariably, there was hyperventilation both at rest and during exercise [24] but, probably due to limitations of the accuracy of the analytic technics, this was not always borne out by elevation of

pH and reduction of CO₂ tension of the arterial blood. (Table III.) Short of diffusion capacity estimations, only three of the more conventional tests led to typically abnormal results: the ventilation equivalent for O₂ was elevated in all but one of our patients at rest (Table III) and in all during exercise [24]; the fraction of carbon monoxide removed (F_{CO}) was reduced in all patients at rest (Table IV) and exercise; and the alveolar-arterial oxygen tension difference (A-a gradient) breathing room air, whenever this was successfully determined, was invariably elevated. (Table IV.) Unfortunately, the first two of these procedures are of little help clinically because equally abnormal values may be due to voluntary hyperventilation in the absence of pulmonary disease. This is not unusual with tests requiring the use of a mouthpiece or mask, it is more common at rest than during activity, and is most frequent in various psychoneurotics and malingerers. It was not a problem in this study because the control group consisted of laboratory personnel who, with the exception of J. K., were well versed in the art of relaxed breathing in spite of mouthpieces, surrounding commotion, and various degrees of external respiratory obstruction. The universal finding of an elevated room air A-a gradient is of little help from the technical standpoint because, if all apparatus and technical know-how is available for this difficult determination, then it is only a small step further to repeat the procedure during low-oxygen breathing for calculation of the D_{O_2} .

Obviously, the present plan of investigation involving diffusion capacity measurements by three different methods at rest and exercise cannot be advocated as a routine for screening when the clinical diagnosis of alveolar-capillary block is entertained. We heartily agree with Forster *et al.* [27] who commented on a similar but more limited project involving the staffs of two research laboratories: "It must be recognized that the determinations of diffusing capacity reported in this paper put considerable strain on the analytical techniques which were available."

Clearly, there was complete separation of normal subjects from patients with alveolar-capillary block by the steady state D_{CO} technic but it must be noted that this test was our major physiologic criterion for inclusion of patients in this report. Were we able to say that all the patients seen in our laboratory who had character-

istic roentgenograms also had demonstrable impairment of diffusion, then the diagnosis of the syndrome would be simplified. However, there were some who otherwise fulfilled the criteria but had no demonstrable diffusion defects (Subject J. V.).

It appears theoretically and in practice that all three methods analyzed in this study represent an estimate of diffusion capacity, albeit under different physiologic circumstances. There were six patients in our series with a single breath D_{CO} within the normal range. On the other hand, there were none in whom this test gave low results in the presence of normal steady state diffusion capacities. The explanation for this must wait until the basic physiologic differences between the single breath and steady state methods have been clarified, and until normal values have been established for these methods in terms of age, sex, stature, and perhaps lung volume.

Considering these technics as diagnostic tools, we believe that if the diagnosis of alveolar-capillary block is considered it can be confirmed by a low D_{CO} with the simple and rapid single breath test. A normal D_{CO} by this method, found in about one-fifth of our cases, although it suggests that the degree of diffusion impairment is not severe, does not rule out the diagnosis. Whether or not, under these circumstances, a steady state D_{CO} or D_{O_2} should be obtained, will depend on available facilities, on the importance of calculating venous admixture, on the advisability of low-oxygen breathing, and on future developments towards simplification of either method.

SUMMARY

This clinical study was undertaken to compare the diffusion capacity of the lungs in man at rest measured by three different methods utilizing carbon monoxide (D_{CO}) and by direct calculation from two-level alveolar-arterial oxygen "gradients" (D_{O_2}); to establish normal values for the D_{CO} methods; and to assess their clinical diagnostic value in patients with diffusion impairment.

Thirty-three patients with alveolar-capillary block syndrome were selected on the basis of (1) diffuse, finely dispersed pulmonary lesions, (2) normal ventilatory function or dyspnea out of proportion to measured ventilatory impairment, (3) diminished diffusion capacity demonstrated by at least two methods, and (4) absence

of physiologic evidence of obstructive emphysema. Diagnoses of beryllium disease, sarcoidosis, chronic interstitial pneumonitis, silicosis, miliary tuberculosis, scleroderma and eosinophilic granuloma were made by lung or other tissue biopsy, on epidemiologic grounds or by bacteriologic study in twenty-four patients, and on clinical grounds alone in nine.

Thirteen normal volunteers were studied as controls by the same methods to establish normal values for the D_{CO} .

Conventional tests consisted of ventilatory function studies including lung volumes, breathing capacities, pulmonary mixing and spirometry; and respiratory studies including determination of arterial and alveolar O_2 tensions, arterial O_2 saturation, CO_2 tension, CO_2 content and pH all during ambient air and low-oxygen breathing.

Diffusion studies included calculation of the D_{O_2} from the data obtained, determination of D_{CO} by the steady state and single breath methods, and calculation of the fraction of carbon monoxide removed (F_{CO}).

The steady state D_{CO} was 19.5 ± 3.2 cc./min./mm. Hg for normal subjects and for the patients averaged 7.0 cc. (range of 2.5 to 13.1); there was no overlap between the two groups. The normal single breath D_{CO} was 30.2 ± 4.6 cc./min./mm. Hg with a mean for the patients of 16.8 (range 4.7 to 28.1) and some overlap. The F_{CO} was more than 50 per cent in all but one normal subject (mean 62 ± 9) and less than 50 per cent in all but one patient (mean 31, range 13 to 50). In eighteen patients the mean D_{O_2} of 9.1 cc./min./mm. Hg compared well with the mean steady state D_{CO} of 7.9 cc./min./mm. Hg (corrected $\times 1.23$ for the greater diffusibility of oxygen) and there was good individual correlation ($r = +0.67$, $P < 0.01$).

During exercise requiring about four times basal oxygen uptake the increase in the mean steady state D_{CO} from 20 to 31 cc./min./mm. Hg in 11 normal subjects was about the same as the rise from 7.5 cc. to 15 cc. in twenty-one patients; all those who were able to exercise were also able to increase their D_{CO} and the discrimination of the test was no better during exercise than at rest.

The theoretic, technical and clinical problems in application of the D_{CO} methods were discussed. Both D_{CO} methods were much more easily performed than the direct D_{O_2} method but only the steady state technic resulted in com-

parable values. Further simplifications of the steady state method may be possible particularly in patients without obstructive emphysema. The single breath test may prove useful for screening studies and, if low, is indicative of impaired diffusion. If it is normal the diagnosis of alveolar-capillary block cannot be ruled out by present standards.

An increasing number of patients are seen with dyspnea or disability out of proportion to the measured mechanical defects of ventilation. The diagnostic and medico-legal importance of diffusion capacity measurements under these circumstances was stressed.

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Effects of Venesection on Pulmonary and Cardiac Function in Patients with Chronic Pulmonary Emphysema and Secondary Polycythemia*

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IT has long been assumed that polycythemia in chronically hypoxic patients with pulmonary emphysema is a compensatory phenomenon. However when heart failure supervenes in emphysema, venesection has been an accepted therapeutic measure since the time of Sir Thomas Lewis.¹ More recently, Harvey, Ferrer and Cournand,² as a result of clinical and physiological study of patients with cor pulmonale, have concluded that venesection is of value not only in the treatment of heart failure but also in the prevention of recurrence of failure after compensation has been restored.

On the other hand, Howarth, McMichael and Sharpey-Schafer³ have opposed venesection in patients with cor pulmonale associated with emphysema even in the presence of heart failure. Their stand is based in part on the reduction in cardiac output and in right auricular pressure found immediately after venesection.

Hecht, Gaylor and Stein⁴ measured oxygen saturation, pulmonary arterial pressure and other respiratory, circulatory and renal functions in eleven patients with cor pulmonale and emphysema before and after venesection and failed to find a uniform response. These authors concluded that venesection may improve subjective symptoms and lower blood viscosity but has no predictable effect on the vascular alterations of cor pulmonale. In an earlier study Lewis, Samuels, Daines and Hecht⁵ had compared findings by similar technics in patients with cor pulmonale due to chronic pulmonary disease with and without secondary polycythemia. They had found a greater degree of arterial

oxygen unsaturation and higher pulmonary artery pressure in the group in whom polycythemia had been corrected. From these two studies venesection does not emerge as a procedure of demonstrated value.

It appears, therefore, that no conclusion in regard to the effects of polycythemia in chronic pulmonary emphysema can be reached from the available data. It has, however, been demonstrated by Harvey, Ferrer and Cournand² that recurrence of heart failure is a rare event when such patients with cor pulmonale who have recovered from an episode of failure are maintained on a program which stresses the combined treatment of heart and lung disease in addition to the prevention of excessive polycythemia. The success of this program suggested to us the possibility that venesection might improve ventilatory function and gas exchange as a result of reduced pulmonary blood volume and pulmonary arterial pressure.

MATERIAL AND METHODS

Eleven male patients hospitalized for chronic obstructive pulmonary emphysema or its complications and found to have secondary polycythemia were studied before and after venesection. The clinical diagnosis was corroborated by the control studies of pulmonary function and blood volume. The patients are listed with blood volume and other data in Table 1. Two plans of study (A and B) were employed and since two of the patients (E. C. and R. B.) were included in both studies, these patients are listed twice. None of the patients was considered clinically to be in heart failure, with a single exception (I. V.). This patient, although still edematous, had been

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treated in the hospital for two and one-half weeks prior to the time of study and in this interval had lost 40 pounds of edema and ascitic fluid with considerable improvement. Of the ten remaining patients one (J. A.) presented no clinical evidence of heart disease, and nine were thought to have chronic cor pulmonale on the basis of clinical, radiologic and electrocardiographic examination.

Effect of a Series of Venesections on Pulmonary Function. Following completion of testing procedures to be described, a series of venesections was performed with ultimate removal of 1 to 3 L. of blood. During this period other medications were continued without change insofar as was possible. Venesections were discontinued either when the hematocrit fell below 50 per cent or after the removal of 2 to 3 L. of blood. The patients were then retested. In six subjects roentgenograms of comparable quality were obtained before and after treatment.

Plasma volume was determined by the method of Gibson and Evans.^{6,7} Vital capacity and expiratory reserve volume were determined spirometrically and inspiratory capacity was calculated from the difference of these values. Functional residual capacity was measured in five subjects by the open circuit method⁸ and residual volume was then calculated. Total lung capacity and the ratio residual volume/total lung capacity $\times 100$ was calculated in four of these patients; in the fifth patient (W. C.) the determination of vital capacity following therapy was unfortunately omitted by oversight. Measurements of ventilation and gas exchange were performed according to the methods of Baldwin, Cournand and Richards⁹ and Riley, Cournand and Donald.¹⁰ In addition, similar measurements were made in three patients during steady state exercise on a motor-driven treadmill employing the same settings of speed and grade following therapy as had been found to be the greatest tolerated during the control study. In three patients during rest and in one patient during exercise in the steady state it was possible to perform two-level oxygen tension studies and thereby calculate the ratio of venous admixture to total pulmonary blood flow ($\dot{Q}_{va}/\dot{Q}_t \times 100$) and diffusing capacity of the lung for oxygen (D_{O_2}). The graphic method of successive approximations described by Riley, Cournand and Donald¹⁰ was used for this purpose.

Arterial blood oxygen content was determined by the method of Van Slyke and Neill¹¹ and oxygen capacity was determined by similar analysis after fifteen minutes of equilibration of blood with air. Fixed corrections of 0.2 volume per cent and 0.6 volume per cent, respectively, were applied to the values for oxygen content and capacity recorded in Table III. Arterial blood pH was measured on a Cambridge pH meter. Arterial oxygen tension (P_{aO_2}) was determined by the method of Riley, Proemmel and Franke;¹² the arterial serum CO_2 content and CO_2 tension (P_{aCO_2}) were calculated from the Henderson-Hasselbalch

equation, employing the line charts of Van Slyke and Sendroy.¹³ Analysis of expired air was determined in the Scholander analyzer.¹⁴

Acute Effect of a Single Venesection on Cardiac Output and Pulmonary Arterial Pressure. Four patients were studied during cardiac catheterization in the course of which 0.5 to 1.0 L. of blood were removed. The catheter was placed in the right auricle (F. C.) or pulmonary artery (remaining three cases) according to the technic of Cournand, Baldwin and Himmelstein,¹⁵ and cardiac output was measured according to the Fick principle by the simultaneous determination of oxygen consumption and arteriovenous oxygen difference. Vascular systolic and diastolic pressures were determined by electromanometers and mean pressures were determined by planimetric integration. Measurements of pressure and blood flow were made both before and fifteen to thirty minutes following venesection. The symbols used follow the recommendations of a group of American physiologists.¹⁶

RESULTS

Effect of a Series of Venesections on Tests of Pulmonary Function. (Tables II to IV). Table II shows that the mean values for all lung volumes measured or calculated were greater after venesection. Spirometrically determined values (inspiratory capacity, expiratory reserve volume and vital capacity) showed small mean changes and the response was variable. In respect to functional residual capacity, residual volume and total lung capacity the post-therapy values were increased in all patients. In each of the five patients tested the increase in functional residual capacity was at least 100 cc. greater than the difference between the duplicate determinations either before or after treatment. Analysis of similar data obtained in this laboratory in a larger series of emphysematous patients indicates that in 95 per cent of tests the values of residual volume and total lung capacity will not vary more than 250 cc. and 350 cc., respectively, during a single testing period. These values were exceeded by the increases in residual volume in three patients and by the increases in total lung capacity in two patients. However, the ratio residual volume/total lung capacity $\times 100$ remained unchanged as did the maximum ventilatory capacity and the index of intrapulmonary mixing.

Total minute ventilation measured either at rest (Table III) or during exercise on the treadmill¹⁷ in the steady state (three subjects, values not recorded) showed no significant differences following treatment. During the one minute of

TABLE I

A. Patients studied before and after a series of venesections											
Patient	Age (yrs.)	Height (inches)	Weight (lbs.)	BSA (M ²)	Plasma Volume (cc/M ² BSA)	Red Cell Mass (cc/M ² BSA)	TBV (cc/M ² BSA)	TBV % Increase Over Predicted	Venesection Total (cc)	% TBV Removed	Hematocrit(%) Before After
Normal					1600	1300	2900	0			45-52
F.S.	57	68	149	1.81	1260	4020	5280	82	2500	26	76 63
E.Co.	55	66	137	1.70	1360	3860	5220	80	2500	28	74 45
W.C.	49	68	121	1.65					2000		70 50
J.A.	49	72	262	2.38	1590	3070	4660	61	3000	27	66 54
R.B.	58	68	113	1.62	1400	2750	4150	43	1500	22	66 42
I.V.	53	68	139	1.75	1850	3470	5320	83	2100	23	65 44
G.L.	62	63	139	1.66	1530	2470	4000	38	2200	33	62 47
A.S.	59	64	180	1.87	1810	2230	4040	39	2000	26	55 47
E.C.	46	67	120	1.62	1710	2010	3720	28	1000	16	54 44
Average	54	67	151	1.78	1560	2990	4550	57	2090	25	65 48
B. Patients studied immediately before and after a single phlebotomy											
R.B.	58	68	113	1.62	1400	2750	4150	43	500	7	66
F.C.	67	66	146	1.74	1750	2280	4030	39	500	7	57
E.C.	44	67	113	1.59	1770	2090	3860	33	500	8	54
H.S.	54	65	160	1.79	1780	2100	3880	35	1000	14	54
Average	56	67	133	1.69	1675	2305	3980	38	625	9	58

TBV = Total blood volume

cc/M²BSA = Cubic centimeters per square meter of body surface area

TABLE II
EFFECT OF VENESECTION ON LUNG VOLUMES, MAXIMUM VENTILATORY CAPACITY AND INTRAPULMONARY MIXING

Patient	Inspiratory Capacity (cc)		Expiratory Reserve Volume (cc)		Vital Capacity (cc)		Functional Residual Capacity (cc)		Residual Volume (cc)		Total Lung Capacity (cc)		RV/TC x 100		Maximum Ventilatory Capacity (L./Min.)		Atr. N ₂ After 7 Minutes O ₂ (%)	
	Before	After	Change	Before	After	Change	Before	After	Change	Before	After	Change	Before	After	Change	Before	After	Change
F.S.	1220	1490	+270	760	1020	+260	1980	2510	+530	3110	3640	+530	2350	2920	+570	4330	5430	+1100
E.Co.	1500	1390	-110	500	480	-20	2000	1870	-130	3690	4010	+320	3190	3530	+340	5190	5400	+210
W.C.				1290	1470	+180				3920	4140	+220	2630	2870	+240			
J.A.	2220	2630	+410	890	930	+40	3110	3160	+50	3400	3610	+210	2510	3080	+570	5620	6240	+620
R.B.	2350	2230	-120	1040	1430	+370	3390	3640	+250	4650	5030	+380	3590	3600	+10	6980	7240	+260
I.V.							1710	1840	+130							27	27	0
G.L.							2300	2360	+60							44	41	-3
A.S.							3040	3330	+270							46	46	0
E.C.	1720	1610	-110	650	540	-110	2370	2170	-200							36	38	+2
Average	1798	1870	+72	858	915	+57	2490	2613	+123	3754	4146	+392	2854	3160	+306	5530	6083	+553

All lung volumes corrected to BTPS

TABLE III

EFFECT OF VENESECTION ON TOTAL VENTILATION AND ARTERIAL BLOOD GASES AT REST AND DURING THE STANDARD EXERCISE TEST

Patient	Rest										Standard Exercise													
	O ₂ Content Vol. %		O ₂ Capacity Vol. %		O ₂ Saturation %		CO ₂ Content Vol. % Serum		pH		P _a CO ₂ mm. Hg		V _E L./Min. /M ² BSA		V _E L./Min. /M ² BSA		O ₂ Saturation							
	Before	After	Change	Before	After	Change	Before	After	Change	Before	After	Change	Before	After	Change	Before	After	Change						
Normal	15-20	16-20			94-98		46-50		7.40		36-40		3.2 ± .6											
F.S.	25.6	21.6	-4.0	29.0	23.2	-5.8	88	93	+5	7.33	7.41	+0.08	70	57	-13	4.3	4.6	+ .3	6.0	9.9	+3.9	72	81	+9
E. Co.	21.8	13.5	-8.3	27.6	16.5	-11.1	79	82	+3	7.33	7.32	- .01	69	75	+6	4.4	4.3	- .1	9.3	11.2	+1.9	62	67	+5
W.C.	18.7	13.7	-5.0	24.3	17.5	-6.8	77	78	+1	7.33	7.32	- .01	54*	50*	-4	4.7	4.6	- .1	9.2	8.4	- .8	72	73	+1
J.A.																3.8	4.5	+ .7						
R.B.	22.4	15.2	-7.2	26.0	17.5	-8.5	86	87	+1	7.41	7.46	+0.05	57	52	-5	5.7	5.5	- .2						
I.V.	20.2	14.1	-6.1	24.4	17.3	-7.1	83	82	-1	7.33	7.37	+0.04	65	63	-2									
G.L.	21.3	16.7	-4.6	24.3	20.2	-4.1	88	83	-5	7.41	7.38	- .03	47	51	+4	6.4	5.6	- .8						
A.S.	19.8	17.7	-2.1	23.6	21.1	-2.5	84	84	0	7.42	7.38	- .04	54	57	+3	5.9	5.7	- .2	9.7	13.2	+3.5	83	84	+1
E.C.	17.8	13.8	-4.0	25.2	18.9	-6.3	71	73	+2	7.45	7.36	- .09	54	60	+6	6.3	6.4	+ .1						
Average	21.0	15.8	-5.2	25.6	19.0	-6.6	82	83	+1	7.38	7.38	0	59	58	-1	5.2	5.2	0	8.6	10.7	+2.1	72	76	+4

* P_aCO₂ by direct method (12).

P_aCO₂ = CO₂ tension

† During one minute of standard exercise

V_E = Minute ventilation

TABLE IV

EFFECT OF VENTILATION ON THE ALVEOLAR-ARTERIAL GRADIENT AND PHYSIOLOGICAL DEAD SPACE AT REST AND STEADY STATE EXERCISE

Studies at Rest		P_{iO_2}		$P_{eA_{O_2}}$		$P_{a_{O_2}}$		$P_{eA_{O_2}} - P_{a_{O_2}}$		$V_D/V_T^c \times 100$		$\dot{Q}_v/\dot{Q}_t \times 100$		D_{O_2}	
Patient	Type of Study	Before	After	Change	Before	After	Change	Before	After	Change	Before	After	Change	Before	After
Normal	Air	146	146		90-110			<15			<30			>15	
W.C.	Two level	174	172	-2	72	88	+16	24	39	+15	58	57	-1		
		149	147	-2	51	53	+2	13	14	+1	61	63	+2	26	>26
J.A.	Breathing air	146	146	0	80	87	+7	28	37	+9	45	46	+1		
R.B.	Breathing air	146	146	0	85	84	-1	26	20	-6	60	60	0		
I.V.	Two level	166	167	+1	87	78	-9	24	20	-4					
		143	145	+2	64	56	-8	14	9	-5				18	20
G.L.	Breathing air	149	148	-1	85	94	+9	25	32	+7	60	54	-6		>30
A.S.	Breathing air	148	147	-1	87	85	-2	33	24	-9	47	51	+4		
E.C.	Two level	166	168	+2	102	91	-11	49	33	-16					
		144	145	+1	88	71	-17	43	25	-18				31	27
Average	Air studies	146	146	0	77	76	-1	26	23	-3	55	55	0		6 10
Studies at exercise on the treadmill in the steady state															
W.C.	1.6 mph 0*	149	147	-2	70	80	+10	38	43	+5	51	47	-4		
J.A.	1.7 mph 6*	172	172	0	97	104	+7	45	49	+4	33	33	0		
		147	146	-1	83	83	0	42	38	-4	28	32	+4	22	27
A.S.	1.0 mph 0*	148	147	-1	90	90	0	25	26	+1	48	49	+1		+1
Average	Air studies	148	147	-1	81	84	+3	33	36	+3	42	43	+1		

 P_{iO_2} = Inspired gas P_{O_2} in mm. Hg B.T.P.S. $P_{eA_{O_2}}$ = "Effective" alveolar P_{O_2} in mm. Hg $P_{a_{O_2}}$ = Arterial P_{O_2} in mm. Hg D_{O_2} = Diffusing capacity of the lungs V_D^c V_T^c $\dot{Q}_v/\dot{Q}_t \times 100$

= Physiological dead space corrected for apparatus dead space in ml. B.T.P.S.

= Tidal volume, corrected for apparatus dead space in ml. B.T.P.S.

= Ratio of venous admixture to total blood flow, expressed as per cent

TABLE V

ACUTE EFFECT OF A SINGLE VENESECTION ON CARDIAC OUTPUT AND PULMONARY ARTERY PRESSURE

Patient	Art. O ₂ Content (vols. %)		Mixed Venous O ₂ Content (vols. %)		A-V Difference (vols. %)		Cardiac Output (L/Min.)		Cardiac Index (L/Min./M ² BSA)		Heart Rate (beats/Min.)		Stroke Volume (cc/beat)	
	Before	After	Change	Before	After	Change	Before	After	Before	After	Before	After	Before	After
Normal	15-20			11-16		4.5			3.1		70		80	
R.B.	21.9 21.2	21.9 21.2	+ .3	17.3 17.0	16.0 17.0	-1.2 +1.4	5.0 5.5	4.0 -1.3	3.1 3.4	2.5 - .8	84 96	-4	56 57	-12
F.C.	16.9 18.0	18.9 +1.4		13.8 14.4	14.9 + .8	3.1 3.6	7.8 6.7	6.3 -1.0	4.5 3.8	3.6 - .6	83 75	-8	94	-10
E.C.	18.8	19.0	+ .2	14.8	14.1	- .7	6.6	4.9	4.1	3.1	110	-2	60	-15
H.S.	18.2 18.0	18.9 + .8		15.1 14.4	13.5 -1.3	3.1 3.6	8.9 8.1	4.8 -3.7	5.0 4.5	2.7 -2.1	92	+8	88	-40

Patient	P.A. Pressure S/D, m(mm. Hg)		B.A. Pressure S/D (mm. Hg)		Ventilation (L/Min. BTPS)		R.Q.		O ₂ Consumption (cc/min.)		Arterial O ₂ Saturation (%)	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Normal	30 10, 15		120 70		5-7		.80		200		94	
R.B.	20 13, 18	10 - 8	95 60	95 62	10.1 9.6	11.7 +1.8	.86 .82	.85 + .1	232 230	235 + 4	85 83	+ 6
F.C.					9.9 10.0	11.2 +1.2	.89 .91	.95 + .5	243 241	250 + 8	74 78	+10
E.C.	28 13, 18	28 13, 21	101 72	108 73	10.0	9.1 - .9	.87	.85 - .2	263	240 -23	85	+ 4
H.S.	55 17, 39	34 15, 22	127 66	95 56	9.5 9.9	10.0 + .3	.80 .81	.90 + .9	277 291	258 -26	81 83	+ 7

standard exercise, however, three of the four patients tested increased their ventilation to higher levels following venesection.

Tables III and IV list the findings of the arterial blood and gas exchange studies. Significant reductions in arterial oxygen content and capacity were found following venesection. The other observations indicate that with the possible exception of the resting diffusing capacity, which was apparently increased following phlebotomy in the three cases studied, there was no improvement in gas exchange for the group as a whole. There were, however, individual instances in which significant changes may have occurred. Resting P_{aCO_2} fell 13 mm. Hg in one patient (E. Co., Table III). Another patient (F. S., Table III) had a 5 per cent increase in resting arterial oxygen saturation and, although the saturation fell following the standard exercise test both prior to and after venesection, the exercise value following therapy increased from 72 to 81 per cent. A third patient (E. C., Table IV) had a rather marked reduction in the elevated $P_{eA}O_2 - P_{aO_2}$ gradient at both high and low levels of oxygenation following venesection. These findings suggest improved gas exchange, but since most of the reduction in the gradient was caused by a fall in $P_{eA}O_2$ as a result of a reduction in alveolar ventilation, there was only a slight increase in the values for arterial oxygen saturation and tension.

In six subjects roentgenograms of comparable quality were obtained shortly before and after the venesection period. In three subjects (E. Co., W. C. and A. S.) there was no change; in three subjects (F. S., G. L. and E. C.) transverse cardiac diameter decreased 1 cm. or more and the pulmonary vascular shadows diminished in density.

Subjective improvement was noted in two subjects (F. S. and J. A.). These patients stated on questioning that breathing was slightly less laborious. The other patients appeared to be neither better nor worse as a result of phlebotomy, although several felt weakened initially. This was thought to be related to the short time interval allowed for venesection.

Acute Effect of Venesection on Cardiac Output and Pulmonary Artery Pressure. (Table V). In each of the four patients studied there was a fall of cardiac output following venesection of not less than 1 L. per minute if changes are computed from the average of the two control determinations. Since oxygen consumption did not change

significantly for the group, this reduction resulted from an increased A-V difference, which in turn was the result of both a higher arterial and lower mixed venous blood oxygen concentration. Stroke volume was decreased following bleeding. Mean pulmonary arterial pressure fell 8 and 17 mm. Hg in two patients and rose 3 mm. Hg in the remaining subject. In contrast to the previous study, a 4 to 10 per cent rise in arterial oxygen saturation was noted in all four patients.

The procedure was well tolerated except in one case. This patient (H. S.) developed a shock-like state after 1,000 cc. of blood were removed. Recovery was uneventful.

COMMENTS

From these studies it is evident that venesection in the emphysematous subject suffering from chronic arterial hypoxia and secondary polycythemia may be followed by an increase in the total lung capacity or its subdivisions. Increases in the functional residual capacity and residual volume appear to be the most consistent changes; it is likely that these increases are caused primarily by a decrease in intrathoracic blood volume. Glaser and McMichael¹⁷ found increases in vital and total lung capacities in a group of normal subjects studied before and after blood donations of 360 cc. In some of our patients a reduction in intrathoracic blood volume is also suggested by decrease in caliber of the pulmonary vessels and reduced heart size on x-ray and by the acute fall in pulmonary artery pressure. Changes in the resistance of the airway to the flow of gases are here considered to be improbable in the absence of any significant change in the maximum ventilatory capacity.

Despite these alterations in the volume of blood and gas in the lungs, there is little evidence in our studies to suggest that either the reduced alveolar ventilation or the uneven distribution of ventilation and blood flow to pulmonary alveoli characteristic of this stage of emphysema is appreciably altered. Following a single venesection there may be an immediate rise in arterial oxygen saturation. This may be the result of a temporary increase in ventilation as observed in the two patients, R. B. and F. C. (Table V). However since a rise in oxygen saturation also occurred in the other two subjects in whom total ventilation fell or rose only slightly, it is also possible that the acute reduction of pulmonary

blood volume may cause a more favorable distribution of capillary blood flow in the lungs. In any event this acute rise in oxygen saturation is apparently not sustained as judged by later studies. One patient (F. S.) who had the greatest increase in lung volumes and in arterial oxygen saturation at rest and after exercise appears as a possible exception. An increase in oxygen diffusing capacity at rest was found in three subjects but is of uncertain significance in view of the small number of patients studied and the many sources of error to which this measurement is subject.

It is unlikely on theoretic grounds that the fall in blood oxygen capacity produced by venesection leads to significant lowering of tissue oxygen tension. This conclusion is based on the calculations of several groups of investigators,¹⁸⁻²⁰ who have demonstrated that in man under conditions causing arterial hypoxia an appreciable elevation of blood oxygen capacity results in only a small increment in the mean systemic capillary oxygen tension.

It is evident, however, from the earlier work of Howarth, McMichael and Sharpey-Schafer³ and from the present study that venesection may result in important changes in the circulation with immediate reduction in right auricular pressure,³ cardiac output and pulmonary artery pressure. At the present time it is not clear whether or not these early effects are sustained. Lewis, Samuels, Daines and Hecht⁵ found higher values for both pulmonary artery pressure and cardiac output in emphysematous subjects without polycythemia than were present in a different but comparable group in whom polycythemia was present. Serial studies in four subjects by Taquini and Fernandez²¹ suggest the possibility that the cardiac output may rise in a compensatory response after a reduction in blood oxygen capacity and content.

From these considerations venesection of patients with emphysema and secondary polycythemia emerges as a procedure which initially may be followed by a rise in arterial oxygen saturation but otherwise has no predictable or considerable effects on dynamic pulmonary function in general and on the arterial blood gas tensions in particular. Its quantitative effect *per se* on tissue oxygen tension as estimated theoretically is probably small. Its value probably lies in the reduction of cardiac output, right auricular pressure and pulmonary artery pressure which can be shown to occur acutely.

The duration of these reductions is not known but the concomitant reduction of right ventricular work may be of therapeutic importance. The experience of Harvey, Ferrer and Cournand² in the treatment and prevention of right heart failure in a large group of patients with cor pulmonale suggests that venesection may be useful as an adjunct to other forms of therapy. Our own experience indicates that while this may be true, the patient in right heart failure usually makes a satisfactory recovery without venesection as long as close attention is given to the other aspects of treatment.

SUMMARY

The effect of venesection on pulmonary and cardiac function was studied in eleven male patients with chronic pulmonary emphysema and secondary polycythemia. While no uniform changes occurred when tests of dynamic pulmonary function were repeated after a series of venesections, it was shown that arterial oxygen saturation rose rapidly in four subjects in whom cardiac output fell and that pulmonary artery pressure fell in two of three subjects tested. It is concluded that while venesection may reduce intrathoracic blood volume, this effect does not usually result in improved ventilatory performance, increased alveolar ventilation or sustained improvement in ventilation-perfusion relationships. Venesection, however, does have appreciable effects on the pulmonary circulation as described. It is not clear whether or not these effects are sustained and the value of the procedure is not established by this study.

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Hydrothorax in Congestive Heart Failure*

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THE problem of the etiology of pleural effusion and of the factors determining the side of its occurrence in patients with congestive heart failure has been a source of interest to physicians for many years. It was noted early that when pleural effusions associated with congestive heart failure occurred unilaterally, they appeared predominantly on the right side. A considerable amount of literature has been accumulated re-attesting this finding and offering a variety of explanations for this phenomenon.

It was noted that the majority of reports concerned with this subject dealt with data derived from clinical material, necropsy findings or roentgenologic findings. Other reports combined the results from any two or all three of these sources of information. A review of the literature has not revealed any report dealing with hydrothorax in congestive heart failure based on a significantly large number of consecutive cases with necropsy examination.

MATERIAL AND METHODS

During the years 1948 through 1953, necropsy was performed at the Mayo Clinic in 402 cases in which congestive heart failure was indicated as either a major or a minor aspect of the patient's final illness. The clinical records were reviewed for data regarding age, sex, confirmation of the diagnosis of congestive heart failure, determination of the presence or absence of cardiac arrhythmia, and to establish the basic cardiac disease underlying the failure. Records of findings at necropsy likewise were reviewed for confirmation of the diagnosis of congestive heart failure, the presence or absence of hydrothorax, the presence of pulmonary infarction, pneumonia, pulmonary edema and the type of heart disease.

When hydrothorax was present, it was first ascertained that neither pleural space was completely obliterated by adhesions. Were such a condition present, it would negate any comparison of the relative incidence of left and right hydrothorax. Cases in which one pleural space was obliterated by adhesions were discarded from the study. Cases also were eliminated

from the study if the amount of fluid in patients with unilateral hydrothorax was less than 250 cc. or if, in patients with bilateral hydrothorax, the side containing the greater quantity of fluid contained less than 250 cc. A minimal requirement of 250 cc. of fluid seemed to be one satisfactory way of distinguishing between patients having hydrothorax with a significant amount of fluid resulting from cardiac failure and those in whom a small amount of pleural fluid may have been the result of agonal accumulation. A total of 290 cases remained for study.

The quantities of fluid in each pleural space were recorded and the cases accordingly were divided into the following three categories based on the features of hydrothorax: (1) bilateral, (2) unilateral right-sided, and (3) unilateral left-sided. The total quantities of fluid found in each pleural space in the 290 patients were determined and from these figures the grand average amount of pleural effusion for the right and left thoracic cavities of the 290 patients was obtained.

The patients were divided into six categories according to the type of heart disease. The categories and the number of patients in each are as follows: (1) coronary artery disease with or without hypertension—one hundred forty-seven patients; (2) hypertensive heart disease—forty-eight patients; (3) mitral valve disease with or without aortic valve disease—thirty-two patients; (4) isolated aortic valve disease—twenty-five patients; (5) myocardial hypertrophy of unknown etiology—fourteen patients, and (6) a miscellaneous group comprised primarily of patients with congenital heart disease or cor pulmonale or both—twenty-four patients.

RESULTS

The ages of the one hundred twenty females ranged from fourteen to ninety years, the average age being 62.5 years. The youngest of the one hundred seventy males was one month of age, the oldest ninety-four years and the average age was 59.8 years.

Of the two hundred ninety patients, twenty-four (8.3 per cent) had unilateral right-sided hydrothorax, eleven (3.8 per cent) had unilateral left-sided hydrothorax, and two hundred

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TABLE I

INCIDENCE AND SIDE OF HYDROTHORAX AND INCIDENCE OF AURICULAR FIBRILLATION AND TYPE OF HEART FAILURE IN PATIENTS WITH HYDROTHORAX OF CONGESTIVE HEART FAILURE ACCORDING TO THE CATEGORY OF CARDIAC DISEASE

	Total No. of Patients	Categories of Cardiac Disease					
		Coronary Artery Disease (with or without hyper- tension)	Hyper- tensive Heart Disease	Mitral Valve Disease (with or without aortic valve disease)	Isolated Aortic Valve Disease	Myocardial Hyper- trophy (etiology unknown)	Miscel- laneous
Side of pleural effusion:							
Right-sided only.....	24	10	4	3	4	1	2
Left-sided only.....	11	5	2	3	0	0	1
Bilateral.....	255	132	42	26	21	13	21
Type of heart failure:							
Right.....	113	55	15	17	9	6	11
Left and right.....	177	92	33	15	16	8	13
Patients with fibrillation:							
Number of patients.....	55	19	10	14	4	3	5
Per cent of total.....	...	13	21	44	16	21	21

fifty-five (87.9 per cent) had bilateral pleural effusion. (Table I.) The average quantity of fluid found in the right hemithorax of all patients in the study was 1,084 cc. The average quantity of pleural fluid in the left thoracic cavity was 913 cc. These two figures represent a ratio of 1.18:1.

Among the two hundred ninety patients with pleural effusion, sixty patients had an associated pulmonary infarction. (Table II.) Among the sixty patients with pulmonary infarction, seven had right-sided effusion only. In four of these seven patients the pulmonary infarct was correspondingly on the right side, and in two, bilateral infarction was present. Only one of the seven patients had contralateral pulmonary effusion and infarction. Of the four patients with unilateral left-sided effusion, one had a pulmonary infarct on the left side and two others had bilateral pulmonary infarcts. In the fourth patient, left hydrothorax was associated with a pulmonary infarct on the right side.

The relationship between auricular fibrillation and the side of the pleural effusion was investi-

gated. (Table II.) Among the twenty-four patients with unilateral right-sided pleural effusion, one (4.2 per cent) had auricular fibrillation. Four of eleven patients (36.4 per cent) with unilateral left-sided pleural effusion had auricular fibrillation. Among the two hundred fifty-five patients with bilateral pleural effusions, fifty (19.6 per cent) had auricular fibrillation.

Among the 290 patients of this study, 177 (61.0 per cent) showed pathologic evidence of pulmonary edema while the remaining 113 did not. (Table II.) Of the twenty-four with unilateral right-sided pleural effusion, fifteen (62.5 per cent) had pulmonary edema; all eleven patients (100 per cent) with unilateral left-sided hydrothorax and 151 of 255 (59.2 per cent) with bilateral hydrothorax also had pulmonary edema.

Fifty-nine patients showed evidence of bronchopneumonia. (Table II.) In twelve patients the pneumonia was limited to the right lung, in ten to the left lung; both lungs were involved in thirty-seven patients. Of the four patients with unilateral right-sided hydrothorax who had pneumonia, three had pneumonia involving

TABLE II
INCIDENCE OF TYPE OF HEART FAILURE, PNEUMONIA, PULMONARY INFARCTION AND AURICULAR FIBRILLATION IN PATIENTS WITH HYDROTHORAX OF CONGESTIVE HEART FAILURE, ACCORDING TO THE SIDE OF HYDROTHORAX

Side of Hydrothorax	Total No. of Patients	Number of Patients with Conditions Associated with Hydrothorax								Auricular Fibrillation
		Heart Failure (type)		Pneumonia			Pulmonary Infarction			
		Right	Left and Right	Right	Left	Left and Right	Right	Left	Left and Right	
Right-sided only	24	9	15	1	1	2	4	1	2	1
Left-sided only	11	0	11	0	0	1	1	1	2	4
Bilateral	255	104	151	11	9	34	20	14	15	50
Subtotal	290	113	177	12	10	37	25	16	19	55
Grand total	290	290		59			60			55

the right lung. In the one patient with unilateral left-sided hydrothorax and pneumonia, the pneumonia involved both lungs. There were fifty-four instances of pneumonia among the patients with bilateral hydrothorax and among these, thirty-four had bilateral pneumonia.

The ratios of patients among the various categories of heart disease who had hydrothorax without pulmonary edema on the one hand and those who had hydrothorax with pulmonary edema on the other hand were similar. (Table I.) Thus, among those with coronary artery disease this ratio was 1:1.7, among those with hypertensive heart disease, 1:2.2 and among those with aortic valve disease, 1:1.8. This ratio was reversed only among the patients with mitral valve disease, being 1.1:1.

REVIEW OF LITERATURE

For many years the common concept has been that the pleural effusion of congestive heart failure is primarily on the right side. A familiar dictum used to be that if a patient had unilateral left-sided effusion, some cause other than heart failure might be responsible.

Attractive theories have been propounded to explain the alleged preponderance of right hydrothorax in congestive failure. Damming back of blood in the right pulmonary vein by a dilated right auricle was thought to be one mechanism.¹ Dock² noted that the center of the

right lung lies nearly 10 cm. below the left ventricle when the patient is in the right lateral recumbent position and the center of the left lung is only 2 to 5 cm. below the left ventricle when the patient is in the left lateral position. Cruchet and Lautier³ attached significance to the preponderance of pulmonary emboli in the right lung. Many clinical observations⁴⁻⁷ supported several of these theories. However, Bedford and Lovibond⁸ from clinical and necropsy data questioned the predominance of right hydrothorax. West⁹ believed that pleural effusions, with few exceptions, were bilateral, ascribing unilateral effusions to some local disease which pinched the large vessels at the root of the lung.

Two basic theories have developed regarding the pathogenesis of pleural effusion: One is based on the assumption that a mechanical obstruction prevents the return of blood to the heart, with resulting transudation of fluid into the pleural spaces. The other theory assumes that the hydrothorax is based on a reaction of the pleura to an inflammatory condition of one or many of the organs that come into contact with the pleura.

Bacelli¹⁰ is traditionally quoted as the first author to express an opinion on the etiology of hydrothorax. He suggested in 1864 that the azygos vein was constricted by being stretched by the downward traction of the right heart and then compressed against the right pulmonary

hilum; others concurred with his concept.^{11,12} Various other causes for compression of the azygos vein also were suggested such as back pressure from superior vena caval stasis,¹³⁻¹⁵ dilatation of the right atrium,¹⁶⁻¹⁹ enlargement of both right chambers,²⁰ dilatation of a branch of the pulmonary trunk²¹ and pressure by the thoracic aorta.²² These concepts have been challenged^{1,14,23} on the basis of anatomic, clinical and necropsy findings.

Esser²⁴ and others^{20,25,26} believed that lymphatic obstruction plus congestion of the pulmonary venous system was an important factor in the formation of pleural effusion. Warren and Stead,²⁷ however, reasoned that, if this theory were correct, lymphatic obstruction would result in a high concentration of protein in the edema fluid. They found that the protein values actually were low.

A later concept that pleural effusion arises not from the parietal but from the visceral pleura was introduced by Fetterolf and Landis,¹ and subscribed to by others.^{3,9} They suggested that compressive action of right and left auricles on the pulmonary veins caused right and left pleural effusion.

An increased negativity of intrathoracic pressure was postulated by some^{22,28-31} to be the factor in drawing fluid from an edematous pleural surface. But others³² disagreed with this theory, and Laha³³ proved by measurements that negativity is decreased in the inspiratory and expiratory intrapleural pressures in congestive heart failure.

Drinker²⁹ subscribed to the theory of increased negativity of intrapleural pressure in congestive failure. He believed an added factor in the production of the pleural effusion was the anoxia associated with the failure which caused an increased capillary permeability of the lungs. Yamada³⁴ performed thoracentesis on several hundred healthy Japanese soldiers and obtained pleural fluid in 29 per cent. As a rule the amount of fluid was small, varying from a few foam bubbles to a few cubic centimeters and rarely more than 20 cc. After these men had performed strenuous physical activity, thereby, according to Yamada, introducing an element of anoxia, pleural fluid was aspirated from 70 per cent of the same group.

Because hydrothorax is found in the same conditions as pulmonary edema (that is, left heart failure, combined left and right failure and mitral stenosis) and is absent or late in

pure right heart failure in which the lungs are spared, pulmonary engorgement was considered to be the essential factor in the production of hydrothorax.^{8,35} Casassa¹⁴ and others^{9,36,37} added corroborative evidence for this theory. However, neither Casassa nor Bedford and Lovibond⁸ had any specific data derived from their own studies with regard to the incidence of pulmonary edema in hydrothorax of congestive failure. Casassa quoted Mouly's work³⁸ wherein the latter found that "acute or subacute" pulmonary edema preceded hydrothorax associated with congestive heart failure in every one of 100 cases.

The theory that inflammation is a causative factor embraces many different mechanisms which have in common an inflammatory process in the pleura or one of the adjacent organs. Influenza, grippe or pneumonitis,³⁹ sclerotic thrombosis of small lobular arteries,^{39,40} an inflammatory process in the wall of the aorta,^{17,20,41,42} pulmonary edema,⁴³ pneumonia,⁴⁴ pericarditis,⁴⁵ perihepatitis^{36,46,47} and a pulmonary, subcortical or pleural embolus^{4,44,45,48,49} have all been suggested as etiologic factors for the hydrothorax of congestive heart failure. Some authors,^{23,50} however, denied the importance of perihepatitis in this association and others⁵¹⁻⁵³ attempted to disprove the relationship of hydrothorax and pulmonary infarction.

Casassa¹⁴ pointed out that if hydrothorax is on an inflammatory basis, the pleural fluid will be high in protein content and if the hydrothorax is on a mechanical basis, it will be correspondingly low in protein content. The finding of low values for protein in the edema fluid by Warren and Stead²⁷ has already been mentioned. Bedford and Lovibond⁸ examined fifty samples of pleural fluid from twenty-seven patients and found that although the specific gravity and protein content in cases of hydrothorax were lower than in a typical effusion caused by inflammation, there was considerable overlapping. They felt that some degree of reaction to inflammation was inevitable since the pleural fluid was in contact with a chronically congested lung.

Another series of contradictions exists in the literature with regard to the relationship between the distribution of hydrothorax and the type of underlying heart disease. For example Barié⁴⁴ stated that pleural effusion occurs more often in mitral heart disease than in aortic heart disease whereas Famulari²² claimed the opposite.

Bedford and Lovibond⁸ concluded from their findings that congestive failure associated with hypertensive heart disease favored a left hydrothorax whereas in rheumatic heart disease, associated mainly with mitral stenosis, right hydrothorax is three times as frequent as left hydrothorax.

Noting the increased frequency with which auricular fibrillation occurred in patients with rheumatic heart disease, and thus mainly in mitral valve disease, Bedford and Lovibond⁸ pointed to the association of isolated right hydrothorax with this arrhythmia. In their series, right hydrothorax occurred almost twice as often with auricular fibrillation as with a normal rhythm.

Both Casassa¹⁴ and Bedford and Lovibond⁸ stressed the preponderance of unilateral left hydrothorax in pure left ventricular failure (twelve of seventeen patients according to Casassa). The latter also found that bilateral hydrothorax was more dominant in patients with both left and right heart failure (forty-six of forty-eight patients or 96 per cent).

COMMENT

In the present study of unilateral effusions the ratio of right effusions to left effusions was slightly more than 2:1; twenty-four patients had effusion of the right pleural space and eleven patients had effusion of the left pleural space. The total series, however, showed that 279 patients had fluid in the right pleural space and 266 had fluid in the left pleural space, so that, although the traditional predominance of right over left hydrothorax is preserved, the difference is much less striking than has been formerly emphasized.

Concerning the various theories on the etiology of hydrothorax our material, based on necropsy findings, could not be used to assess the theories based on anoxia of pulmonary tissue and increased negativity of intrathoracic pressure. We believe that the theory of compression of the azygos vein has been satisfactorily refuted.

Experimental evidence⁶⁴ has shown that the maintenance of pleural effusion is a remarkably dynamic process. By the use of water labeled with deuterium oxide it has been found that the total volume of the pleural effusion in a patient whose congestive failure was on the basis of hypertensive heart disease was completely replaced within an hour. In other words, stagna-

tion of pleural fluid did not occur, the fluid was in circulation constantly. Lymphatic obstruction alone could not account for an actively forming and reforming effusion.

In the present study pulmonary edema was found to be present, both grossly and microscopically, in 177 of 290 patients (61 per cent) with hydrothorax on the basis of congestive failure. It would seem logical to assume that if hydrothorax were secondary to pulmonary edema, an overwhelming percentage of patients would have pulmonary edema. Certainly the figure 61 per cent is significant and suggests that the presence of pulmonary edema might have some bearing on the production of hydrothorax, but its absence in 39 per cent of the patients would discourage the belief that it is the only explanation for the development of hydrothorax.

We were not able to find a consistent correlation between the presence of pleural effusion and of various inflammatory processes which might conceivably irritate the pleura to the extent that it would cause pleural effusion.

In the present study either gross or microscopic evidence of pneumonia was found in fifty-nine patients and was thus absent in 231 patients. (Table II.) Among these fifty-nine patients little or no correlation existed between the side of the pleural effusion and that of the pneumonia. In twenty-one instances pleural effusion was associated with unilateral, contralateral pneumonia. (Table II.) But since pneumonia was present on the same side as pleural effusion in only thirty-eight of two hundred ninety patients, it is apparent that the theory of pneumonic infection as the basis for the pleural effusion of congestive heart failure is not tenable.

In the present study changes in the liver, which could be interpreted as representing perihepatitis, were observed in four instances and pericarditis occurred in seven patients.

In twenty-four of the sixty patients who had associated pulmonary infarction (Table II) hydrothorax was contralateral to a unilateral pulmonary infarct. There was a positive correlation between the side of the pulmonary infarct and the side of the pleural effusion in thirty-six patients.

In the present study four patients with hypertensive heart disease had unilateral right-sided effusion and two had unilateral left-sided effusion. (Table I.) Forty-two patients had bilateral effusion. Among the patients with mitral valve disease, three had effusion on the left side, three

had effusion on the right side and twenty-six had bilateral effusion. It can be seen from these data as well as from the corresponding figures for other types of heart disease (Table I) that left hydrothorax does not predominate over right hydrothorax in any one type of heart disease. In addition, contrary to the findings of others, in our series we found a greater preponderance of pleural effusion on the right side in patients with coronary artery disease and hypertensive heart disease.

Our findings showed that 44 per cent of the patients with mitral valve disease had auricular fibrillation, whereas the incidence of fibrillation in the other categories of heart disease varied from 13 to 21 per cent. (Table I.) Nevertheless, of twenty-four patients with unilateral right-sided hydrothorax only one was associated with auricular fibrillation, whereas this cardiac arrhythmia was present in four of eleven patients with unilateral left-sided hydrothorax.

Among the eleven patients with unilateral left-sided hydrothorax, none had the pleural effusion alone; all eleven had combined pleural effusion and pulmonary edema. (Table II.) Considering the twenty-four patients who had unilateral right-sided hydrothorax, nine (37.5 per cent) had pleural effusion without pulmonary edema and fifteen (62.5 per cent) had pleural effusion and pulmonary edema. Of 255 patients with bilateral pleural fluid, 151 (59.2 per cent) had combined left and right failure.

From our data we are unable to identify any one predominating factor as the cause of pleural effusion on the basis of congestive heart failure.

Goldman and Bassett,⁵⁵ in a study of two patients with congestive heart failure, produced peripheral edema in both patients by supplementing the diet with sodium before an elevation of the brachial venous pressure was demonstrable.

It is difficult to compare data derived from necropsy material with that derived from clinical material. As Bedford and Lovibond⁸ have pointed out, the incidence of bilateral hydrothorax is much higher in the necropsy room than it is in the ward. There are two possible explanations for this discrepancy. First, it is possible that hydrothorax begins on one side and when the patient is examined, this primary manifestation of heart failure is seen. With treatment, the effusion may disappear. With inadequate re-

sponse to treatment the effusion may become bilateral terminally, and is recognized as such only at necropsy. Lack of technics for the detection of small amounts of effusion or the difficulty in identifying loculated effusions may also account for the clinical preponderance of unilateral hydrothorax.

Furthermore, it is of questionable value to compare our data with the five series reported in the literature, which were based wholly or in part on necropsy material. In the patients studied by Steele,¹⁸ three had obliteration of one pleural space. In the series of Bedford and Lovibond,⁸ hydrothorax was interpreted as representing 300 cc. or more of fluid. Neither author observed the criterion of the other, however, and in the three other series^{7,56,57} neither of these criteria was used. As mentioned earlier, we believe it is impossible to assess the significance of hydrothorax when the opposite pleural space is obliterated. We do not believe, as stated previously, that quantities of fluid of less than 250 cc. are of particular significance (1) because of the difficulty of measurement and (2) because any amount less than 250 cc. may represent transudation of fluid secondary to an agonal state.

We eliminated 102 patients on the basis of these two criteria. In forty-two instances one pleural space was completely obliterated by adhesions, and in seventy-one instances hydrothorax was present but the amount of fluid was less than 250 cc. In eleven patients, both of these conditions existed.

SUMMARY

- At autopsy, of 290 patients with hydrothorax due to congestive heart failure, twenty-four had unilateral right-sided hydrothorax, eleven had unilateral left-sided hydrothorax and 255 had bilateral hydrothorax. Thus, the incidence of right and left hydrothorax was approximately equal as 279 of the 290 patients had right-sided hydrothorax and 266 patients had left-sided hydrothorax.

In every category of heart disease except mitral heart disease, combined left and right failure predominated over right failure only. In our series auricular fibrillation was more commonly associated with unilateral left-sided hydrothorax than with unilateral right-sided hydrothorax.

Percentage-wise, pulmonary edema was more frequently encountered among those patients with unilateral pleural effusion on the left side than among those with unilateral pleural effusion on the right side.

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The C-Reactive Protein Determination as an Index of Myocardial Necrosis in Coronary Artery Disease*

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THE C-reactive protein is an abnormal serum globulin which is formed by the body in response to infection, tissue necrosis and neoplasia.¹⁻⁷ It is called C-reactive protein because it forms a precipitate with the somatic C-polysaccharide of the pneumococcus.¹ Previous studies have shown that a positive test for C-reactive protein is a non-specific but sensitive indicator of inflammation of infectious or non-infectious origin.⁵⁻⁷

Other investigators and the authors have found the test to be a reliable index of myocardial inflammation in rheumatic fever.⁸⁻¹⁰ Recently our preliminary studies have shown that serum C-reactive protein may also serve as an index of myocardial necrosis and inflammation in coronary artery disease.¹¹⁻¹³ The observations reported in this paper confirm our previous studies and indicate that the positive C-reactive protein test is a valuable aid in establishing the presence of significant myocardial necrosis in symptomatic coronary artery disease.

MATERIAL AND METHODS

One hundred patients with coronary artery disease were selected for this study. This number is but a fraction of the hundreds of patients whose serums were tested since 1954, when the C-reactive protein determination was first applied by the authors to detect myocardial necrosis.¹¹ There were fifty-five patients without Q waves in the electrocardiogram who may be designated as having suffered from coronary insufficiency¹⁴ or coronary failure¹⁵ as distinct from typical transmural infarction. Six of these fifty-five patients had gastrointestinal disease which complicated the clinical picture. There were thirty-four patients with

typical transmural infarction and Q waves in the electrocardiogram and five patients in the premonitory phase of such infarction. Six patients with old transmural infarction and a positive C-reactive protein test were also included.

A patient was considered to have myocardial necrosis when the clinical picture included such features as fever, leukocytosis, elevated blood fibrinogen and an elevated sedimentation rate in the presence of changes in the electrocardiogram.¹⁴⁻¹⁶

In these studies, the rabbit antiserum precipitin technic of Anderson and McCarty⁸ was used. C-reactive protein rabbit antiserum† and the patient's serum, 1.5 cm. of each, were drawn up into a capillary tube (external diameter about 1 mm.) and incubated for two hours at 37°C. The degree of precipitation (0 to 4 plus) was read after overnight refrigeration. Each millimeter of precipitate was considered 1 plus. The corrected sedimentation rate was performed according to the technic of Wintrobe. The blood fibrinogen was determined either by chemical analysis of the fibrin clot by the method of Kingsley¹⁷ or by the recently developed spectrophotometric clot density method of Losner and associates.¹⁸ Serial determinations were made on bloods drawn at frequent intervals.

RESULTS

Transmural Myocardial Infarction (Thirty-four Cases). The C-reactive protein determination was positive in all thirty-four patients with transmural myocardial infarction. All these patients presented a typical clinical picture and electrocardiographic findings which included Q waves and progressive RS-T and T wave changes. A positive test for C-reactive protein was obtained within twelve to seventy-two hours

† The rabbit antiserum was generously supplied by Schieffelin and Company.

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after the onset of pain. C-reactive protein disappeared from the serum as early as the second week of illness but in some patients it persisted for four to five weeks. The latter were usually severely ill and had persistent low-grade fever. Serial negative tests were the rule late in the course of the disease, despite persistent elevation of the sedimentation rate. A positive test for C-reactive protein, after it had become negative during convalescence, usually indicated a complication such as phlebothrombosis, acute gout and progressive or acute recurrent myocardial infarction.

The C-reactive protein determination was positive (1 plus) twelve hours after the onset of pain in the case of a seventy year old white woman. Postmortem examination confirmed the presence of transmural myocardial infarction of the posterolateral and posteroseptal walls.

The following case report illustrates the clinical correlations in acute transmural infarction.

CASE 1. I. A., a sixty-seven year old executive, suffered from obesity, mild diabetes mellitus (not requiring insulin), labile essential hypertension, and recurrent acute gouty arthritis of the right big toe relieved by colchicine. In the year before the present illness he had suffered a "stroke" characterized by "double vision." There were also one or two episodes of brisk nosebleed associated with elevation of the systolic blood pressure to over 260 mm. Hg.

In November, 1954, a routine electrocardiogram showed minimal RS-T depression in V₆ as the sole possible abnormality. (Fig. 1.) On June 1, 1955, the patient experienced some substernal and left costal margin pain lasting but a few minutes. An electrocardiogram revealed an almost iso-electric T wave in aV₁ and lowering of the T wave in V₅ and V₆. A diagnosis of coronary artery disease was made and the patient was advised to rest at home. Because there were no further symptoms, he continued with his usual daily routine. On June 3, 1955, he suffered for three hours with more severe "burning" substernal pressure which radiated to the left shoulder and inner aspect of the left arm as well as to the back. On June 4, 1955, the electrocardiogram showed distinct RS-T depressions in leads I, II, aV₁, and V₆ with a tendency for the T wave to be diphasic. The QT interval was prolonged and there was a negative U wave in lead I, aV₁ and V₆. (Fig. 1.) The patient continued to be ambulatory after subsidence of the pain.

On June 7, 1955, the patient was afebrile and asymptomatic. The heart sounds were good. The ventricular rate was 60 per minute. A₂ was greater than P₂. The blood pressure was 160/100. The blood urea nitrogen was 17.0 and the uric acid 7.9 mg. per cent. The corrected sedimentation rate was 19 mm./

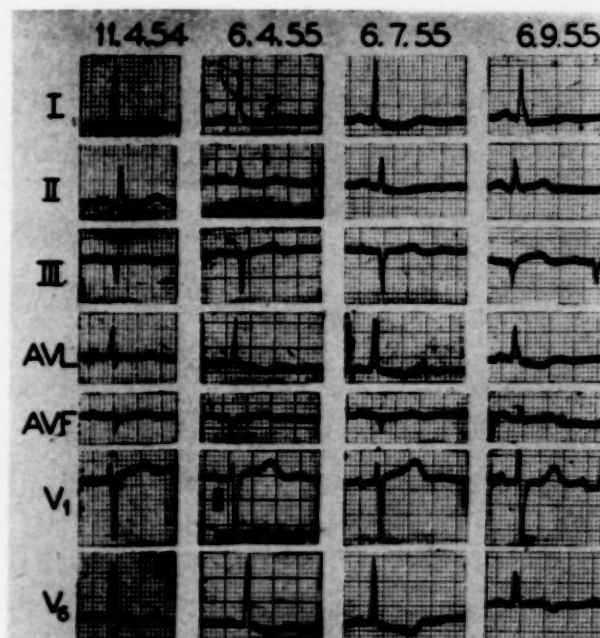


Fig. 1. Case 1. Premonitory phase of coronary occlusion with transmural infarction. RS-T and T wave changes, prolonged QT interval and inverted U waves. Slight RS-T elevations, June 9, 1955. C-reactive protein test: negative.

hr. (Wintrobe). The hematocrit was 50 per cent. The C-reactive protein determination was negative.

On June 9, severe substernal pain recurred and lasted four hours. The electrocardiogram now showed a high take-off of the RS-T segment in leads II, III, aV_f, V₅ and V₆. The T waves were less inverted in V₅ and V₆. (Fig. 1.) The blood sugar was 227, uric acid 7.8, urea nitrogen 16.6, and fibrinogen 300, all in mg. per cent. The corrected sedimentation rate was 6 mm./hr. (Wintrobe). The hematocrit was 55 per cent. The prothrombin time was thirteen seconds with a control of twelve seconds. The C-reactive protein determination was again negative.

There was recurrence of pain for three hours on June 10. The heart sounds were good. The ventricular rate was 75 per minute. The blood pressure was 134/100. The temperature was 101°F. The R wave in V₁ became tall. The T waves were inverted in leads I, II, aV₁, V₅ and V₆. (Fig. 2.) On June 11, there was slight substernal discomfort. The blood pressure was 128/90. The ventricular rate rose to 90/min. and the first mitral sound became split. The T waves became upright in leads I, II, aV₁, aV_f, V₅ and V₆ with RS-T elevation in V₆ and V₇ and a Q wave in V₇. (Fig. 2.) By June 12, there was marked weakness and the blood pressure had fallen to 112/90. The electrocardiogram on June 13, showed RS-T elevation in the standard leads, aV_f, V₆ and V₇, with a QS wave in V₇. (Fig. 2.) The temperature was 100.6°F. and the corrected sedimentation rate had risen to 27 mm./hr. (Wintrobe). The blood fibrinogen had risen to 1100

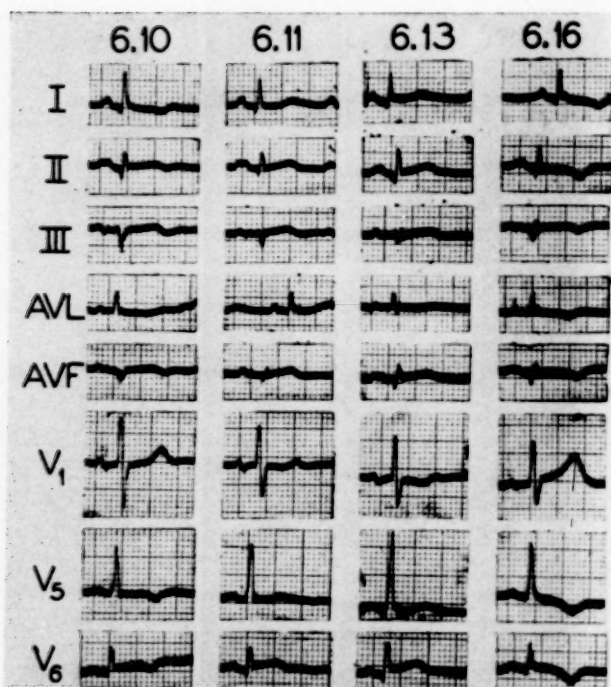


FIG. 2. Case 1. Coronary occlusion with transmural infarction involving the diaphragmatic and lateral walls of the left ventricle. Serial changes in the standard and extremity leads, tall R wave in V1, RS-T elevation and T wave inversion in V6. QS in V7 not shown.

mg. per cent. The C-reactive protein was *positive* (1 plus). The white blood cell count was 8,000 per cu. mm., with 66 per cent polymorphonuclears, 26 per cent lymphocytes, 5 per cent monocytes and 3 per cent eosinophils. Anticoagulant therapy was instituted with phenindione. Colchicine (0.6 mg. twice a day) was administered prophylactically to prevent an attack of gout.

Fever with temperatures of 100 to 101.2°F. persisted for six days. By the eleventh day the fibrinogen was normal (390 mg. per cent) but the C-reactive protein test was still positive (trace). (Fig. 3.) The sedimentation rate continued to increase despite the normal blood fibrinogen and *negative* C-reactive protein test on the thirteenth and fourteenth days of illness. By the fifteenth day the electrocardiogram showed the chronic serial changes of infarction. T1, T2 and T3 were inverted, as were the T waves in aVf, V5, V6 and V7. The T waves were taller in leads V1 to V4. (Fig. 4; vide June 25.)

The patient was asymptomatic after the first week of illness. His blood pressure was 110 to 122/70 to 84. The patient decided to discontinue his prophylactic colchicine on June 18. On June 27 and 28, the sixteenth and seventeenth days of illness, the C-reactive protein test again became *positive* (1 plus). The blood fibrinogen was still within normal limits (390 mg. per cent and 408 mg. per cent). The patient complained of a drawing pain in the left lower extremity but there was no objective evidence of gouty inflam-

mation. By June 30, there was a full-blown acute gouty arthritis of the metatarsal-phalangeal joint of the left big toe, characterized by pain, tenderness, heat, redness and swelling. By this time the C-reactive protein test was strongly positive (2 plus). The fibrinogen was slightly elevated (462 mg. per cent).

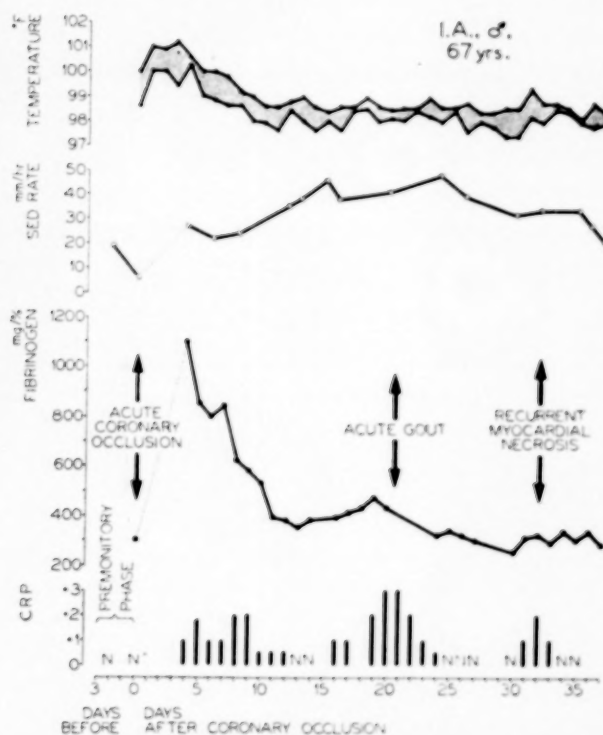


FIG. 3. Case 1. Course of coronary occlusion and transmural infarction. Good correlation between C-reactive protein and blood fibrinogen during first ten days. C-reactive protein was more sensitive than blood fibrinogen to the acute changes of gouty arthritis and of recurrent myocardial necrosis during convalescence.

The sedimentation rate was still in the 40 mm. range as before the attack. (Fig. 3.)

Four doses of colchicine (2.4 mg.) were given daily from June 30 to July 2 to the point of diarrhea. There was subjective symptomatic improvement but redness, heat and slight tenderness remained. From July 3 to July 5, 400 mg. phenylbutazone were given daily without remarkable objective change. C-reactive protein test remained strongly positive. Despite therapy the joint was still minimally red and slightly tender on the seventh day of the gouty attack. On this day the C-reactive protein test was still positive (trace) but the blood fibrinogen had fallen to the normal level of 318 mg. per cent.

On July 6, the joint was minimally tender and very faintly red. The C-reactive protein test was *negative* and the blood fibrinogen continued to be normal (336 mg. per cent). Thereafter, the patient was given daily maintenance doses of colchicine (1.2 mg.).

On July 10, substernal pain radiating down the

left arm and lasting one hour occurred after excessive exertion. The patient was apprehensive. The first sound at the mitral area was again split. The blood pressure was 170/110. On July 11, the patient was asymptomatic. The blood pressure had returned to the previous level of 120/70. An electrocardiogram showed T wave inversion in aVL (Fig. 4.) The temperature had risen to 99.6°F. the afternoon before the onset of pain but the remainder of the course was afebrile and asymptomatic. The blood fibrinogen was normal and the C-reactive protein test was negative. However, thirty-six hours after the onset of pain the C-reactive protein test became positive and remained positive for three days. On the other hand, the sedimentation rate did not increase and the blood fibrinogen remained normal.

Comment: Despite electrocardiographic changes (Fig. 1) and pain during nine days of the premonitory phase (June 1 to 9), the C-reactive protein determination, sedimentation rate and blood fibrinogen were normal. (Fig. 3.) Typical electrocardiographic changes of coronary occlusion and transmural infarction were noted on June 11 after two more days of pain. (Fig. 2.) These changes were associated with only a slightly elevated sedimentation rate, a markedly elevated blood fibrinogen and a positive C-reactive protein determination. It will be noted that the C-reactive protein determination was still positive (trace) when the fibrinogen had reached normal levels on the eleventh day, indicating greater sensitivity of the C-reactive protein determination in this case. The disparity between the continued elevated sedimentation rate and the negative C-reactive protein determination and normal blood fibrinogen is apparent on the thirteenth and fourteenth day of illness. (Fig. 3.)

It will be noted that a positive C-reactive protein determination heralded an acute attack of gout at a time when the sedimentation rate was lower and the blood fibrinogen was normal. On the seventh day of acute gouty arthritis the C-reactive protein test was still positive, but the blood fibrinogen was normal, again indicating the greater sensitivity of the C-reactive protein determination. (Fig. 3.)

On the thirty-first day of illness recurrent chest pain after exertion was associated with electrocardiographic changes. (Fig. 4.) A positive C-reactive protein determination was the only indicator of recurrent myocardial necrosis. It should be noted that there was no significant rise in body temperature, the blood fibrinogen remained normal and the sedimentation rate constant.

Coronary Insufficiency with Negative C-reactive Protein Determination (Thirty-five Cases). The C-reactive protein determination was repeatedly negative in thirty-five patients with clinical and electrocardiographic evidence of coronary artery disease but without distinct criteria for myocardial necrosis. The clinical picture varied

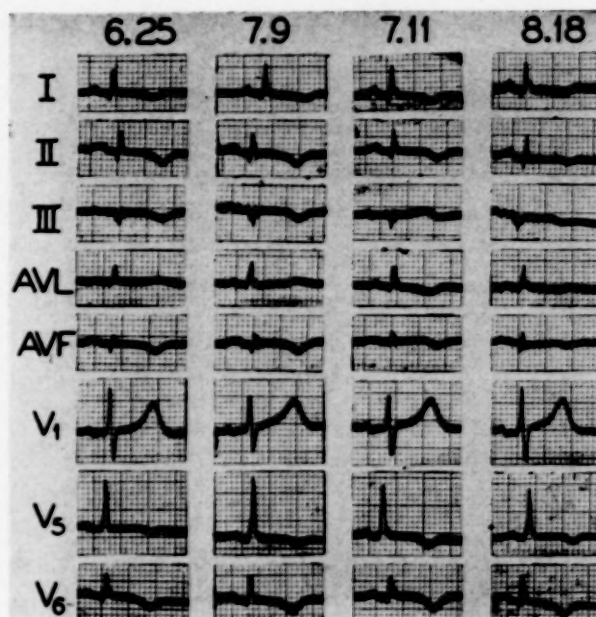


FIG. 4. Case I. Recurrent myocardial necrosis during convalescence from coronary occlusion. T wave inverted in aVL. C-reactive protein test became positive, fibrinogen remained normal and sedimentation rate was unchanged.

from that of mild angina of effort to that of severe angina, dyspnea and orthopnea. The electrocardiographic findings similarly ranged from RS-T and T wave changes to those of marked left ventricular hypertrophy, right and left bundle branch block, complete heart block and old transmural infarction. In some patients the clinical picture was complicated by either chronic gallbladder disease, hiatus hernia, peptic ulcer or hypothyroidism. A negative C-reactive protein determination indicated the absence of myocardial necrosis and was of diagnostic value particularly in the more symptomatic patients with marked electrocardiographic changes, in the patients with old transmural infarction and in those with both gastrointestinal and coronary disease. The following case report of a patient with spontaneous acute coronary insufficiency illustrates the findings in this group. (Fig. 5.)

CASE II. I. G., a fifty-three year old white man, experienced for the first time moderate substernal pain radiating to the left shoulder. These episodes of pain continued with increased frequency for the next three days. Physical examination was non-contributory. The blood pressure was 110/80. The patient was kept at chair rest for two weeks, during which time the electrocardiograms showed T wave changes in the standard leads and V6, and deep T wave inversions in V3 and V4. These changes were

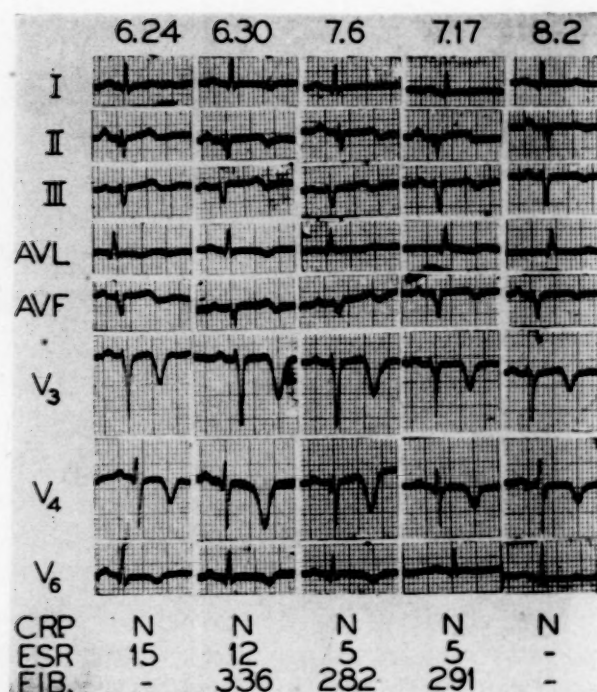


FIG. 5. Case II. Coronary insufficiency with negative C-reactive protein test. Marked electrocardiographic changes unassociated with any abnormality in C-reactive protein, sedimentation rate or blood fibrinogen.

associated with an afebrile course, a normal white cell count, normal sedimentation rates and blood fibrinogens and negative serial C-reactive protein determinations. The patient's symptoms subsided after the first few days of rest. He returned to work as a house painter after two weeks and has been asymptomatic for one year.

Comment: The marked electrocardiographic changes suggested a more serious illness. However, the consistently negative C-reactive protein determinations indicated the absence of significant myocardial necrosis.

Coronary Insufficiency with Positive C-reactive Protein Determination. (Twenty Cases). The positive C-reactive protein determination in this group of twenty cases was an index of myocardial necrosis. In six patients with both coronary disease and either chronic peptic ulcer, hiatus hernia or gallbladder disease, the positive test indicated that the symptoms were of myocardial origin. The next case report illustrates a positive test in a patient with acute complete heart block and an unstable idioventricular rhythm.

CASE III. E. B., an eighty year old white woman with a history of hypertensive and coronary heart disease and mild diabetes, was first seen on April 14, 1955, two months before admission. At that time she was digitalized because of bilateral basal rales and

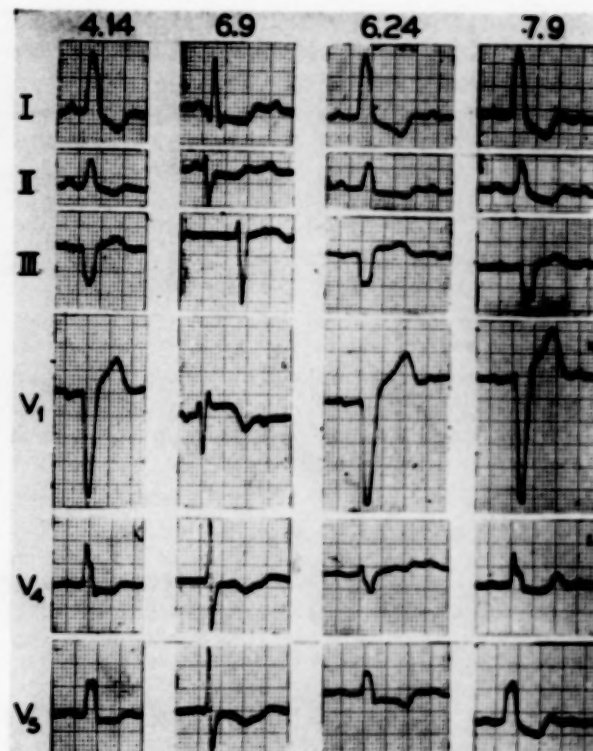


FIG. 6. Case III. Sinus rhythm and left bundle branch block changing to complete and then 2:1 A-V block. Unstable idioventricular focus.

hepatomegaly. Fluoroscopic examination revealed that the heart was enlarged to the left and the aorta was tortuous. The electrocardiogram showed regular sinus rhythm and left bundle branch block with T1 inverted and T2 diphasic. The T waves in V1 and V2 were upright. There were RS-T depressions and diphasic to inverted T waves in V4, V5 and V6. (Fig. 6.)

On June 9, 1955, the patient experienced marked weakness, but no substernal pain. An electrocardiogram showed complete heart block with a right bundle branch block pattern. The T waves were deeply inverted in the precordial leads. (Fig. 6.) She was hospitalized on June 10, with the diagnosis of complete heart block and an unstable idioventricular focus as pacemaker, in all likelihood secondary to a silent myocardial infarction. By June 14, 1955, the electrocardiogram had stabilized to a 2:1 block, the pattern reverting to left bundle branch block. The QRS was more widened now and measured 0.16 seconds. The T wave had become more deeply inverted in lead II and in the left precordial leads. (Fig. 6.) These electrocardiographic changes were not associated with substernal pain or fever. The sedimentation rate varied from 29 to 33 mm./hr. (Wintrobe) and the C-reactive protein determination was negative on repeated occasions.

On June 19, the T waves became inverted in V2 and V3. The tall R wave disappeared from V3, V4

and V5. By June 21, the changes had reverted. However, on June 24, there were short runs of 3:1 block and again the R wave became extremely low in V3 and V4 (Fig. 6.). By June 26, the tall R waves returned in V3 and V4. These electrocardiographic changes were followed by a positive C-reactive protein

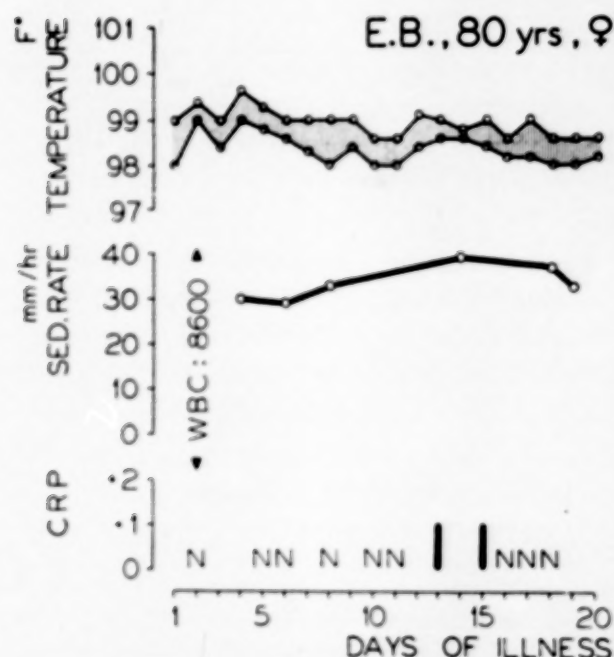


FIG. 7. Case III. Positive C-reactive protein determination in the presence of a minimal elevation of sedimentation rate and afebrile course in a patient with acute complete heart block and unstable idioventricular focus.

determination which lasted three days. The sedimentation rate had risen but very slightly to 39 mm./hr. (Wintrobe). The patient never experienced substernal pain or fever. The white blood cell count was always within normal limits. (Fig. 7.)

Comment: In this patient the C-reactive protein determination was diagnostic of myocardial necrosis, in the presence of complete heart block and bizarre electrocardiographic changes. It was negative at the onset of the acute heart block presumably because of absence of significant muscle necrosis. The test was valuable because the course was otherwise asymptomatic and afebrile. The C-reactive protein served as a guide for ambulation in the presence of a persistently elevated sedimentation rate.

The next case report illustrates the value of the positive C-reactive protein test for the diagnosis of myocardial necrosis in spontaneous coronary insufficiency where the electrocardiogram showed only RS-T and T wave changes.

CASE IV. L. G., a forty-three year old white physician, experienced severe substernal pressure, belching and nausea two days before he was seen on June 8,

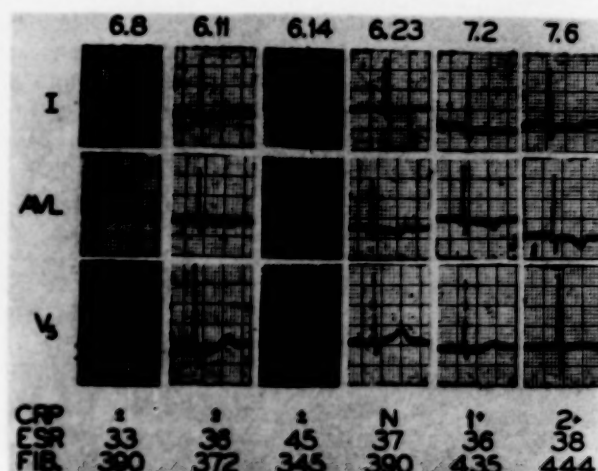


FIG. 8. Case IV. Spontaneous acute coronary insufficiency with myocardial necrosis. C-reactive protein was positive but fibrinogen was normal June 8 through June 14. C-reactive protein was negative when sedimentation rate was persistently elevated June 23. C-reactive protein was again positive and fibrinogen elevated without change in sedimentation rate July 2 through July 6.

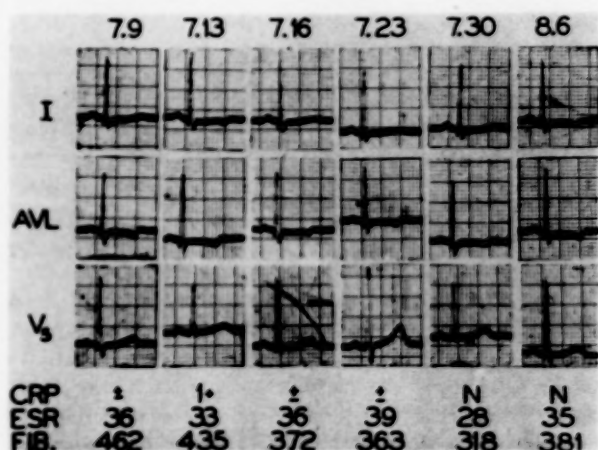


FIG. 9. Case IV. Recurrence of acute coronary insufficiency after exertion. C-reactive protein was positive for one week after fibrinogen was returned to normal July 16 through July 23 and was negative after recovery, despite a persistently elevated sedimentation rate.

1954. Physical examination was non-contributory. The electrocardiogram showed RS-T depressions and T wave inversions in leads I, aV1, V5 and V6. (Fig. 8.) The first white cell count was 11,750 per cu. mm. Subsequent white cell counts were normal. There was no fever. The sedimentation rate showed an elevation in the first week. The C-reactive protein test was slightly positive, the blood fibrinogen was normal. The patient was kept at chair rest at home. At the end of two weeks (June 23, 1954) the electrocardiogram had improved. The C-reactive protein test was negative, the blood fibrinogen was normal, but the sedimentation rate was still elevated. (Fig. 10.)

In the next few days the physician returned to his

rigorous schedule and complained of some substernal discomfort. For the next seventeen days the C-reactive protein determination was again positive. The blood fibrinogen was elevated. The sedimentation rate remained elevated at its previous level and did not show any change. The C-reactive protein test was positive

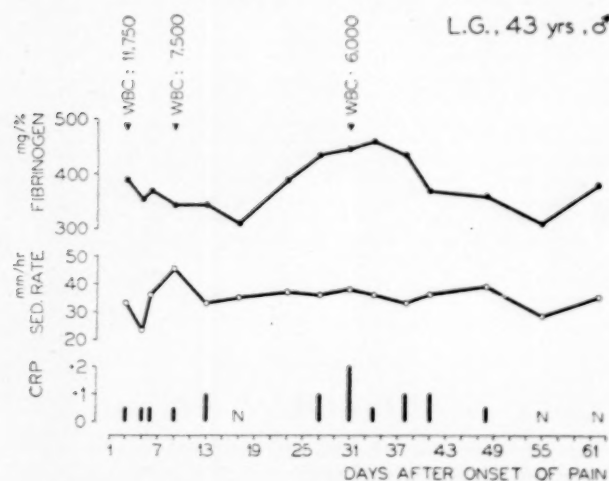


FIG. 10. Case IV. Acute coronary insufficiency with myocardial necrosis. C-reactive protein was more sensitive than fibrinogen at onset. Positive C-reactive protein paralleled elevated fibrinogen during recurrence, despite lack of change in sedimentation rate. C-reactive protein was positive longer than fibrinogen (forty-ninth day) and became negative despite a persistently elevated sedimentation rate during convalescence (sixty-first day).

for one week after the blood fibrinogen had returned to normal levels (below 400 mg. per cent). (Figs. 9 and 10.)

Comment: This case illustrates the greater sensitivity of the C-reactive protein determination in the diagnosis of myocardial necrosis in a patient with spontaneous acute coronary insufficiency. The test was informative at the onset when the blood fibrinogen was normal and the white cell count was equivocally elevated (Fig. 10). The CRP determination paralleled the blood fibrinogen during the recurrence of symptoms but showed greater sensitivity, remaining positive at a time when the blood fibrinogen was normal. The sedimentation rate and white cell count during this period did not change and were not diagnostic.

Premonitory Phase of Coronary Occlusion with Negative C-reactive Protein Determination (Five Cases). Five patients were studied early in the premonitory phase of acute coronary occlusion. The C-reactive protein determination was negative during the period of RS-T and T wave changes but became positive as transmural infarction developed. The first case report illustrates this feature. (Figs. 1 and 3.)

One patient with recurrent substernal pres-

sure of two weeks duration finally experienced an acute infarction on the day after admission and died suddenly before Q waves developed in the electrocardiogram. The C-reactive protein test was negative six hours before death. Postmortem examination was not obtained.

Old Transmural Infarction with Positive C-reactive Protein Determination (Six Cases). Recurrence of pain in six patients with previous myocardial infarction was associated either with no change or with RS-T and T wave changes in the electrocardiogram, which showed the Q wave of the previous infarction. A positive test distinguished these cases from those symptomatic cases of old infarction without recent necrosis.

COMMENTS

The diagnosis of coronary occlusion and transmural infarction is made by history, clinical findings and the electrocardiogram, which is characterized by Q waves, RS-T elevations and serial RS-T and T wave changes. The C-reactive protein determination is unimportant for the diagnosis of infarction under these circumstances. However, it may be important in the diagnosis of complications during convalescence. Serial determinations included in this paper show that the serum C-reactive protein is a more sensitive indicator of an acute complication during convalescence than the sedimentation rate and the blood fibrinogen. The C-reactive protein test becomes negative when the sedimentation rate may be persistently elevated even during convalescence. The C-reactive protein test can therefore become positive again with an acute change, whereas the sedimentation rate may not rise significantly above its already high level.

The diagnosis of symptomatic coronary artery disease without Q waves in the electrocardiogram, such as coronary insufficiency or coronary failure, is made by the history of anginal pain and the associated electrocardiographic findings. RS-T and T wave changes characterize the usual subendocardial injury but the injury may be reversible and not lead to myocardial necrosis.

Our studies indicate that a positive C-reactive protein test is a valuable aid in establishing the presence of irreversible injury and significant myocardial necrosis in this group of patients. Our observations confirm and extend those of Löfström¹⁹ and Hedlund⁷ who demonstrated acute phase protein (C-reactive protein) in the serums of patients with myocardial infarction but not in patients with arteriosclerotic heart

disease and angina, chronic valvular disease and essential hypertension.

As in Hedlund's series, C-reactive protein determinations were negative in our patients with uncomplicated peptic ulcer, chronic cholecystitis and cholelithiasis, and hiatus hernia. Thus in symptomatic patients with both coronary disease and gastrointestinal disease, and an abnormal electrocardiogram, a positive C-reactive protein test indicates that the symptoms are of myocardial origin. The test is similarly useful in determining the presence of recent recurrent myocardial necrosis in patients with electrocardiographic changes indicative of an old transmural infarction.

The limitation of the C-reactive protein determination is its non-specificity. It may be used in evaluating a patient with coronary disease only when other infectious or non-infectious stimuli for its formation are known to be absent. Our own observations and those in the literature indicate that the time of appearance and extent of the sensitive C-reactive protein response are related to the degree of the stimulus.^{7,19-21} A negative test may be obtained in the presence of mild, acute or subacute inflammation, or there may be a delay in the appearance of a positive test after a mild acute process. Serial tests are therefore necessary before a negative C-reactive protein determination is considered representative of either no necrosis or clinically insignificant necrosis.

SUMMARY AND CONCLUSIONS

1. C-reactive protein determinations in 100 selected patients with coronary disease indicate that the level of C-reactive protein in the serum is a sensitive index of myocardial necrosis and inflammation, provided other infectious and non-infectious stimuli for its formation are absent.

2. The C-reactive protein test is negative in the premonitory preinfarction stage of acute transmural infarction.

3. C-reactive protein may be detected in every case of transmural myocardial infarction with Q waves in the electrocardiogram. Serial tests are essential because there may be a delay (twelve to seventy-two hours) in the formation of C-reactive protein, depending on the degree of infarction.

4. A negative test during convalescence from transmural infarction (third or fourth week) is thought to signify subsidence of myocardial

necrosis and inflammation. Any recurrence of a positive test indicates phlebothrombosis, recurrent myocardial infarction or some other complication.

5. A positive C-reactive protein test is diagnostic of myocardial necrosis in symptomatic coronary disease without Q waves. The test is sensitive and clinically helpful when the usual objective criteria for myocardial necrosis are equivocal or absent, such as fever, leukocytosis, elevated sedimentation rate and blood fibrinogen.

6. A negative C-reactive protein test in coronary insufficiency indicates the absence of significant myocardial necrosis only if repeated serial determinations are negative.

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Hypochromic Anemia with Hyperferricemia Responding to Oral Crude Liver Extract*

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RECENTLY, two patients have been observed with a type of anemia which, to our knowledge, has not been previously described. This anemia was refractory to therapy with known hematopoietic substances including iron, vitamin B₁₂, folacin and leucovorin, but responded maximally to the oral administration of liquid extract of liver, U.S.P. (Valentine).†

Common hematologic findings in these two patients included the following: (1) The peripheral blood showed erythrocytic anisocytosis, poikilocytosis and anisochromia. The calculated mean corpuscular hemoglobin concentrations were consistently low, whereas the mean corpuscular volumes varied between microcytosis and normocytosis. (2) The bone marrow demonstrated erythroid hyperplasia with erythroblastic maturation arrest. Abnormal erythroid maturation similar to that seen in the marrow of patients with untreated pernicious anemia was not apparent. (3) The serum iron concentrations were elevated with markedly increased saturation of the total serum iron binding capacity. In each instance, the anemia was of long duration and continuing study failed to reveal an adequate explanation for its development and persistence.

CASE REPORTS

CASE 1. P. J., a thirty-eight year old white radio repairman, was first admitted to Crile Veterans Administration Hospital in February, 1953, with symptoms and signs of severe anemia. His history dated from 1944 when, while still in the Navy, he was hospitalized because of anemia, for which no cause was apparent. Since dyspepsia had been a complaint

† Obtained from the Valentine Company, Inc., Richmond 9, Virginia.

and since the anemia was hypochromic, a presumptive diagnosis of bleeding duodenal ulcer was made. During the period of hospitalization, however, no evidence of blood loss was found. Therapy at the time consisted of blood transfusions. He was discharged from the service in August, 1945. During the succeeding eight years, he remained asymptomatic. Three months prior to his admission to Crile Hospital, he noted the onset of increasing fatigue, exertional dyspnea and pallor, and diminished activity tolerance. Past history revealed that as a youth, he sometimes was unable to engage in active sports because of fatigability. Except for the episode of anemia while in the service, however, he had never been severely incapacitated. On the advice of physicians, he had taken ferrous sulfate, 1.0 gm. daily, since discharge from the Navy. He was not aware of any familial history of anemia. Dietary habits were good and there was no history of alcoholism.

Physical examination, except for tachycardia and pallor of the skin and mucous membranes, was unremarkable. The liver was not enlarged, the spleen was not palpable and there was no significant lymphadenopathy. No signs of deficiency of B-complex vitamins were apparent.

Laboratory studies revealed a hypochromic anemia. The hemoglobin was 6 gm. per 100 cc. There was no evidence of blood loss or increased hemolysis. Leukocytes, thrombocytes and reticulocytes were normal. Peripheral blood films revealed marked erythrocytic anisocytosis, poikilocytosis and anisochromia. Wright-stained films of bone marrow were interpreted as follows "... hyperactive erythropoiesis with maturation arrest as evidenced by increased numbers of megaloblasts and early erythroblasts. Abnormal myelocytes and erythroblasts seen in pernicious anemia are not present ... "‡

‡ Interpreted by Dr. David R. Weir, then attending hematologist at Crile Veterans Administration Hospital.

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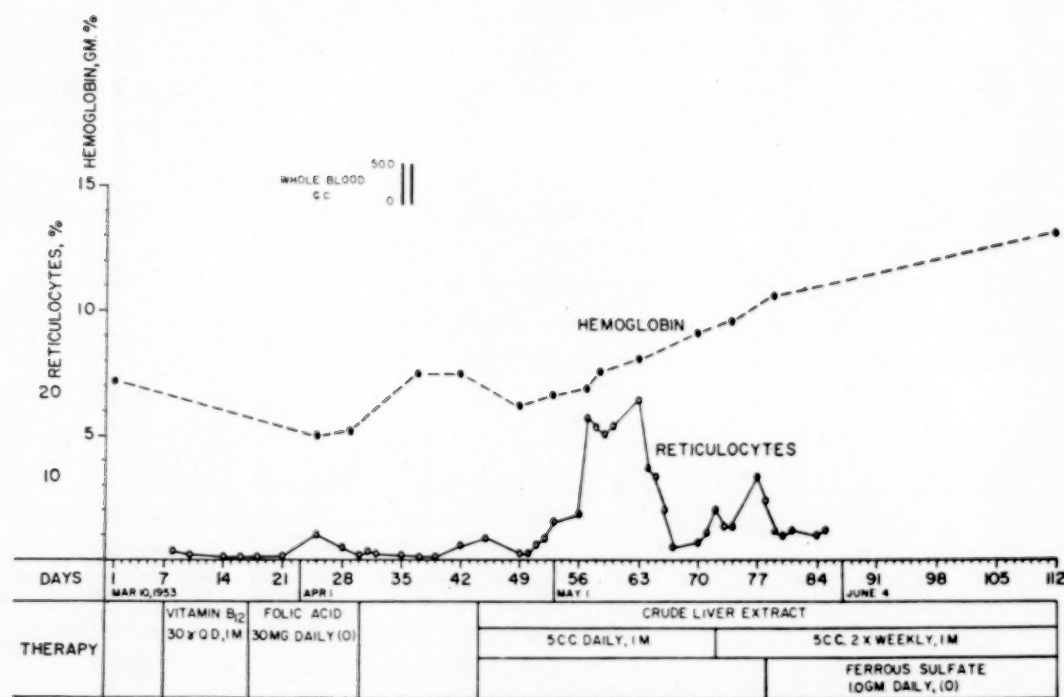


FIG. 1. Case I, P. J. Graph showing failure of hematologic response to vitamin B₁₂ and folacin. Response to an initial course of intramuscular crude liver extract is shown.

The clinical course during this first hospitalization is shown in Figure 1. The administration of vitamin B₁₂, 30 µg. intramuscularly, daily for ten days, and folacin, 30 mg. orally, daily for two weeks, produced no response. He was then given intramuscular crude liver extract, 5 cc. daily. A reticulocyte response

TABLE I
CHART SHOWING PERCENTAGE OF NUCLEATED
ERYTHROID CELLS IN BONE MARROW

	Case I (P. J.)	Case II (E. S.)
Proerythroblasts	6.8%	2.8%
Erythroblasts	26.2%	34.8%
Normoblasts	1.1%	8.2%
Myeloid/erythroid ratio	2/1	1.2/1

occurred, becoming apparent on the eighth day of therapy and reaching a peak of 19 per cent on the nineteenth day. With this response, the hemoglobin rose from 7 to 13 gm. per 100 cc. in the succeeding two months.

After one month of daily intramuscular crude liver extract, the dose was decreased to 5 cc. twice weekly; ferrous sulfate, 1 gm. daily, was also given. The patient was discharged from the hospital in June, 1953. Although this schedule of therapy was continued on an

out-patient basis the anemia recurred and he returned to the hospital in November, 1953.

At this time, the anemia was again hypochromic and microcytic. The erythrocyte count was 2.5 million per cu. mm., the hemoglobin, 5.5 gm. per 100 cc.; and the hematocrit 20 per cent. The mean corpuscular volume was 80 cubic microns, and the mean corpuscular hemoglobin concentration, 27 per cent. The total leukocyte count was 7,400 per cu. mm.; differential leukocyte count showed 61 per cent polymorphonuclear leukocytes, 34 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. Reticulocytes and thrombocytes were normal. The previously described morphologic abnormalities of the erythrocytes were again apparent. Bone marrow again showed erythroid hyperplasia with erythroblastic maturation arrest. (Table I.)

Continuing studies again failed to reveal the etiology of the anemia. There was no evidence of blood loss either symptomatically or by laboratory study. Repeated examinations of the stool were negative for blood. Radiographic examination of the entire gastrointestinal tract was negative. Serum iron concentration during relapse was 226.6 µg. per 100 cc.; the serum iron binding capacity was completely saturated.*

* We are indebted to Dr. E. S. Bowerfind, Department of Medicine, Lakeside Hospital, Cleveland, Ohio, for the serum iron determinations. Normal values in this laboratory for serum iron and for serum unsaturated iron binding capacity are 95 ± 26 µg. per 100 cc. and 230.6 ± 37 µg. per 100 cc., respectively.

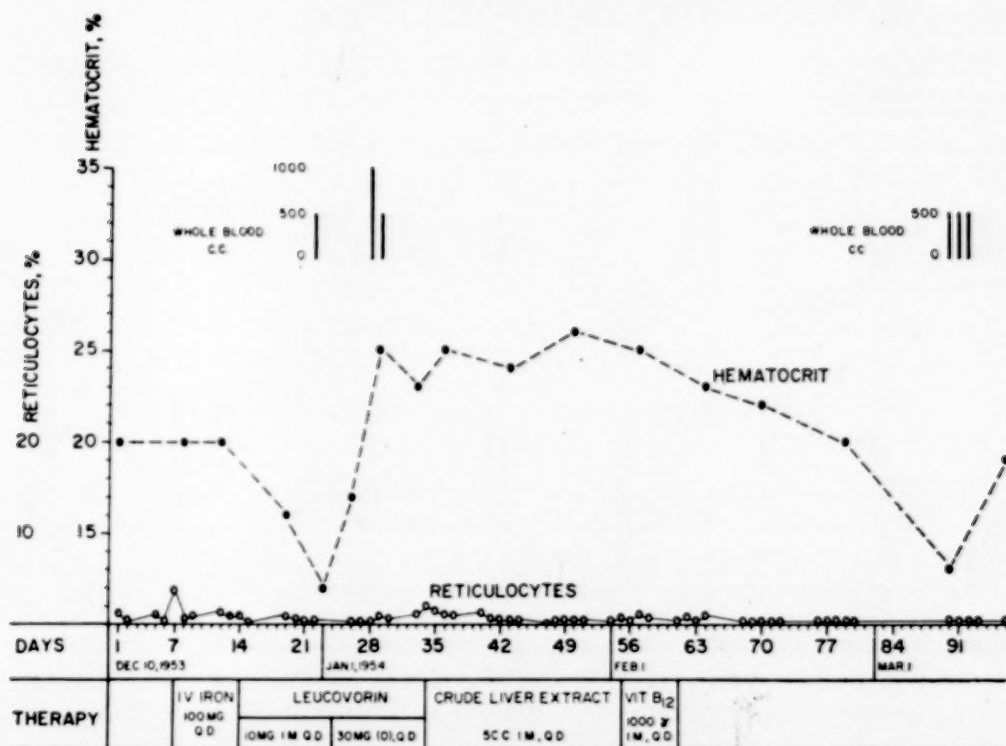


FIG. 2. Case 1. Graph showing failure of response to intravenous iron, leucovorin, a second course of intramuscular crude liver extract and large doses of intramuscular vitamin B₁₂.

Various tests seeking evidence of possible increased hemolysis were performed. Direct Coombs' test, electrophoresis of hemoglobin, alkaline denaturation for estimation of fetal hemoglobin, Donath-Landsteiner test, Ham test and osmotic fragilities of erythrocytes before and after twenty-four hours of sterile incubation at 37°C. were normal. No hemolysins or agglutinins were demonstrated in the patient's serum in the pH range from 6.5 to 7.5; serum cold agglutinins were present in a dilution of 1:4. Mechanical fragility of erythrocytes was slightly increased; 7.3 per cent hemolysis occurred at zero time and 31.2 per cent hemolysis occurred after sterile incubation of the cells at 37°C. for twenty-four hours. (Normal values are 2.6 ± 0.8 per cent at zero hour, and 10.6 ± 3.5 per cent after incubation.) The radiochromate erythrocyte autosurvival time was shortened. The half life of the labelled erythrocytes was twenty-eight days; all were eliminated from the circulation in eighty-nine days.

Evidence of intestinal malabsorption was not found. Free hydrochloric acid was present in fasting gastric contents. The oral glucose tolerance test and the plasma prothrombin concentration were normal. There was no history of diarrhea. No evidence of abnormalities of hepatic or renal function were found.

The hematologic course during this hospitalization is shown in Figure 2. Therapy with saccharated oxide of iron, 100 mg. intravenously, daily for seven days was without effect. The administration of leucovorin,

10 mg. intramuscularly daily for ten days, and calcium leucovorin, 30 mg. daily orally for ten days, produced no response. Intramuscular crude liver extract, 5 cc. daily for three weeks, was then given—this time without response. Vitamin B₁₂ in doses of 1,000 μg. intramuscularly daily for six days was also ineffective.

The failure of the patient to respond to this course of therapy with intramuscular crude liver extract suggested the possibility that the preparation did not contain an active hematopoietic substance present in a preparation administered six months previously. Furthermore, a more consistent source for such a substance might have been found in a cruder liver preparation. Accordingly, the patient was then given liquid extract of liver, U.S.P. (Valentine).

The hematologic response to the oral administration of this preparation in doses of 30 cc. three times daily is shown in Figure 3. Prompt reticulocyte response occurred with a peak of 25 per cent on the ninth day of therapy. Erythrocytic regeneration was rapid with a rise in the hematocrit from 21 to 42 per cent in seven weeks. With this response, the mean corpuscular hemoglobin concentration rose from 25 to 30 per cent. Subjective improvement also was prompt. Increased feeling of well-being had occurred within forty-eight hours after beginning therapy.

After two months of therapy, the oral crude liver extract was discontinued. Five and one-half months after cessation of therapy, hematologic relapse had

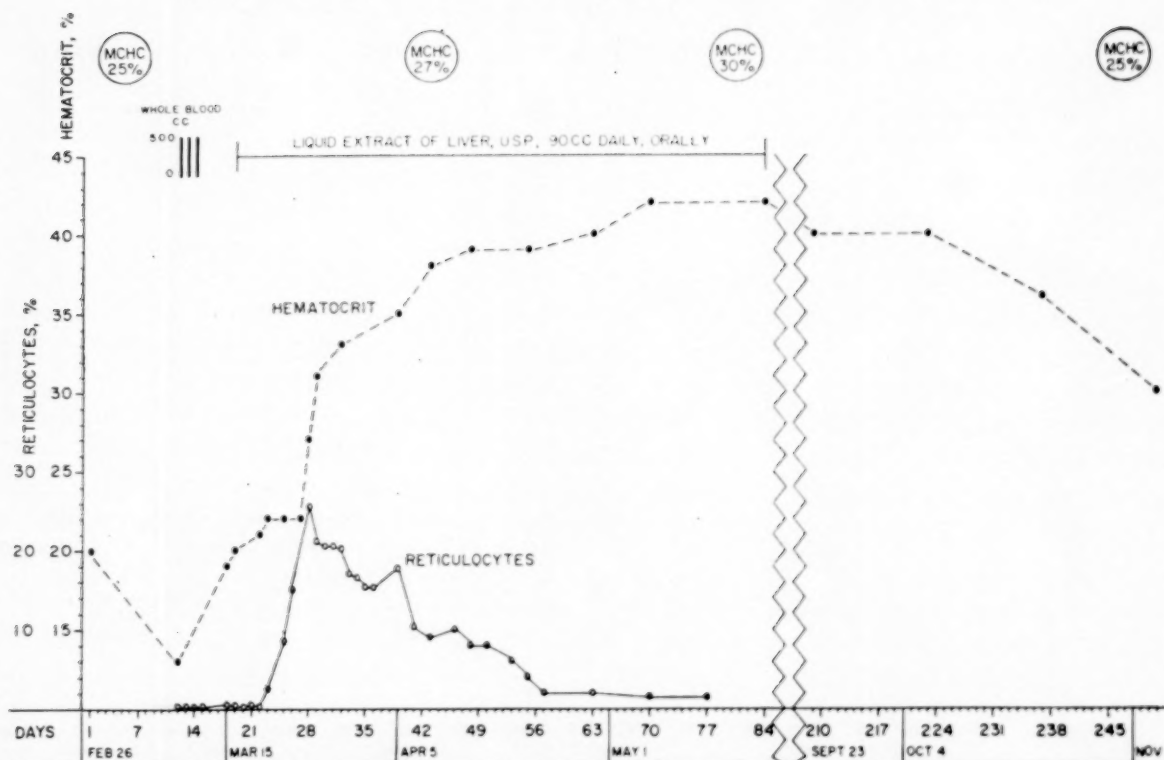


FIG. 3. Case I. Graph showing hematologic response to liquid extract of liver, U.S.P. (Valentine), in oral doses of 90 cc. daily.

occurred; the hematocrit had fallen to 30 per cent and the mean corpuscular hemoglobin concentration to 25 per cent.

In later trials of therapy (Fig. 4.), the patient failed to respond to 30 cc. of the crude extract given in a single daily dose for ten days. A suboptimal response occurred with 45 cc., given in three divided doses daily for ten days. Reticulocyte response occurred with a peak of 15 per cent on the eighth day of therapy. The hematocrit rose to only 39 per cent after twenty-one days and had fallen to 33 per cent only twenty-five days after cessation of therapy.

The subsequent responses of this patient have indicated the hematopoietic activity of various fractions prepared from the crude liver extract in an attempt to isolate the active material. These studies, when completed, will be reported at a later date.

CASE II. E. S. is a forty-one year old Negro man in whom the diagnosis of anemia was first made in 1946 while he was in the Army. The anemia was hypochromic and microcytic. Complete study at that time failed to reveal positive evidence of blood loss; no cause for anemia could be demonstrated. During six months of hospitalization prior to discharge from the Army, therapy with iron and intramuscular liver extract failed to influence the course of the anemia.

He was first admitted to Crile Veterans Administration Hospital in November, 1949. From then until

1954, he was hospitalized six times for attempted treatment and for investigation concerning the etiology of his moderately severe anemia. Continuing observation, however, failed to reveal an adequate cause. The calculated erythrocytic corpuscular indices revealed consistent hypochromia and a variation between normocytosis and microcytosis. Marked erythrocytic anisocytosis, poikilocytosis and anisochromia with increased numbers of target cells were constantly noted on examination of peripheral blood films. Leukocytes and thrombocytes were normal.

During this period, therapy with oral iron, folacin, intramuscular crude liver extract and vitamin B₁₂ failed to influence the course of the anemia in this patient. The amounts of these substances administered were those normally effective in patients with the types of nutritional anemia due to specific deficiencies. During one hospitalization, when the hemoglobin fell to less than 4 gm. per 100 cc., whole blood transfusions were given. Otherwise, during this five year period of observation, the hemoglobin level remained between 6 and 9 gm. per 100 cc. Symptomatically, the patient did well at these levels requiring only moderate restriction of activities.

This patient is a chronic alcoholic and drinks excessively during week-ends. During these drinking bouts, his food intake is markedly curtailed but it is fairly adequate during periods of relative abstinence.

Physical examination revealed average develop-

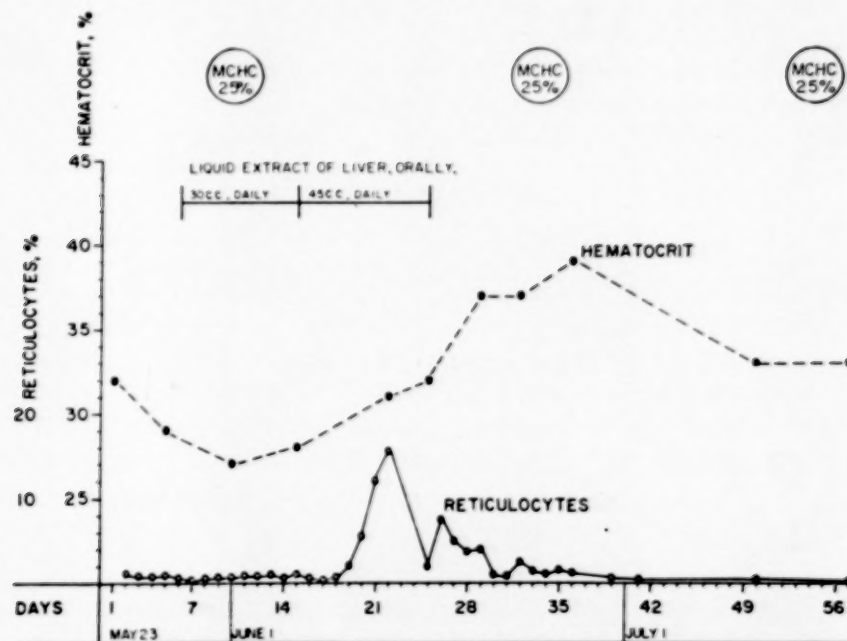


FIG. 4. Case 1. Graph showing failure of response to liquid extract of liver, U.S.P. (Valentine), in oral doses of 30 cc. daily. Suboptimal response is shown with daily doses of 45 cc.

ment and state of nutrition. The liver was enlarged and palpable 6 cm. below the right lower costal margin; the edge was smooth and slightly tender. Splenomegaly was first noted in 1952; the spleen has been palpable 4 cm. below the left lower costal margin since that time. There was no lymphadenopathy. The skin and mucous membranes showed no evidence of a vitamin deficiency state. No neurologic abnormalities were present.

Laboratory studies failed to reveal adequate cause for this persistent anemia. No evidence of blood loss or of increased hemolysis was found. Although radiographic examination showed a deformity of the duodenal bulb, no ulcer crater was visualized. Repeated examinations of the stool for blood were negative. The osmotic fragility of the erythrocytes was decreased. Serum bilirubin and urine urobilinogen levels were normal. Sickling of erythrocytes did not occur and the direct Coombs' test was negative. Paper electrophoresis of hemoglobin revealed a normal pattern. There was no familial history of anemia; so far as the patient was aware, all his progenitors were of African descent.

Needle biopsy of the liver demonstrated fibrosis and hemosiderin deposition consistent with a pathologic diagnosis of "pigmentary cirrhosis." This finding, along with elevated serum iron levels and near total saturation of the iron binding capacity (*vide infra*), made tenable a clinical diagnosis of hemochromatosis. Abnormalities in liver function tests indicated deterioration of hepatic function during the five year period of observation. Thymol turbidity increased from 3 units in 1949 to 14 units in 1954. Serum globu-

lin rose from 3.3 to 5.2 mg. per 100 cc., while serum albumin fell from 5.8 to 3.9 mg. per 100 cc. during the same period. Bromsulphalein retention has varied

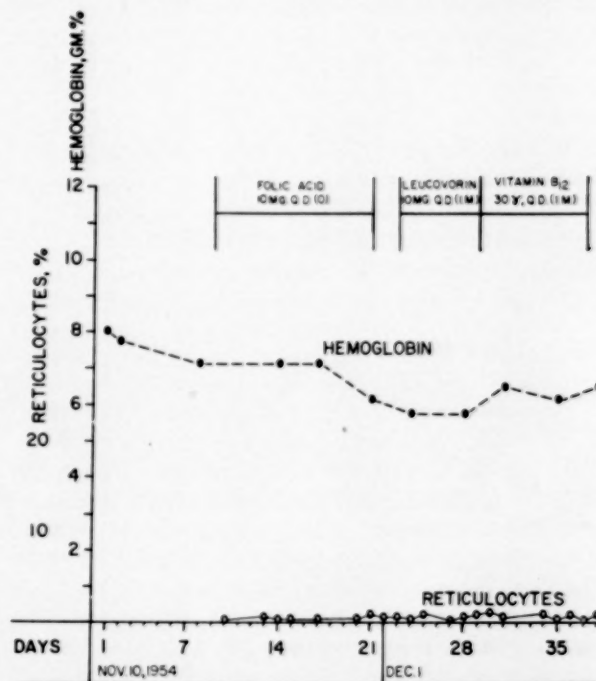


FIG. 5. Case II, E. S. Graph showing failure of hematologic response to folacin, leucovorin and vitamin B₁₂.

from 4 to 16 per cent in forty-five minutes. Cephalin flocculation has been consistently 3 plus to 4 plus in forty-eight hours. Serum levels of alkaline phosphatase

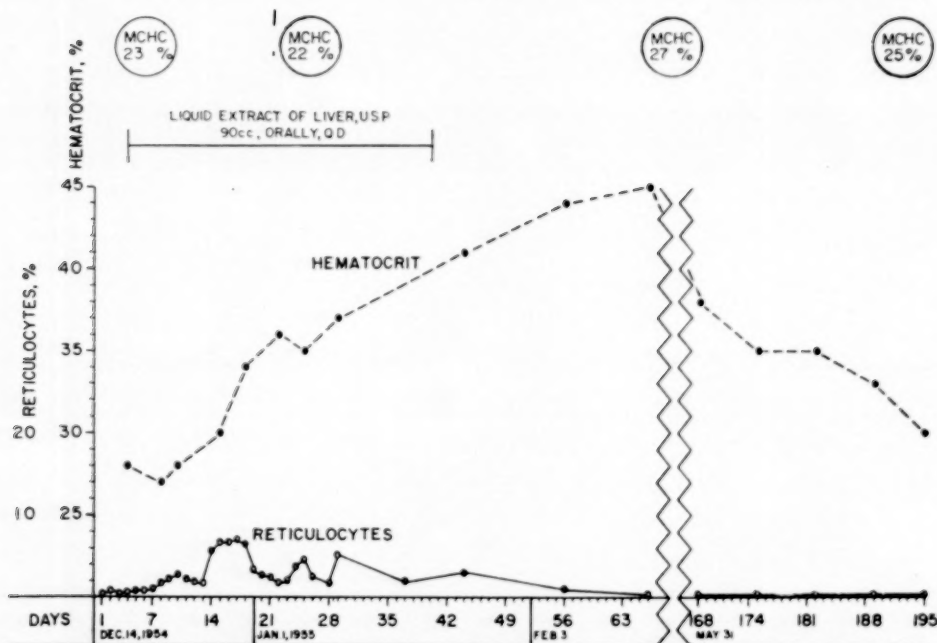


FIG. 6. Case II. Graph showing hematologic response to liquid extract of liver, U.S.P. (Valentine), in oral doses of 90 cc. daily.

tase, bilirubin and cholesterol, and the plasma prothrombin concentration have remained within normal limits.

Histamine-fast achlorhydria has been demonstrated repeatedly in this patient. The oral glucose tolerance test was normal. Although evidences of mild hypertensive vascular disease have been present, tests for renal function have been repeatedly within normal limits.

In November, 1954, the patient was readmitted to the hospital because of the persistence of symptoms of anemia. Laboratory findings revealed: Erythrocyte count, 3.9 million per cu. mm.; hemoglobin, 8 gm. per 100 cc.; hematocrit, 35 volume per cent. Leukocyte count was 14,700 per cu. mm.; differential leukocyte count showed 73 per cent neutrophils, 14 per cent lymphocytes, 11 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. Erythrocytes showed the morphologic abnormalities previously described. The mean corpuscular volume was 89 cubic microns, and the mean corpuscular hemoglobin concentration, 23 per cent. Reticulocytes and thrombocytes were normal. The bone marrow showed erythroid hyperplasia with maturation arrest at an erythroblastic level. (Table I.) Repeated studies again showed no evidence of blood loss or of increased blood destruction. The serum iron concentration was 249.6 μ g. per 100 cc. and unsaturated iron binding capacity was 25.9 μ g. per 100 cc.²

Treatment with folacin orally, 10 mg. daily, for two weeks, with leucovorin intramuscularly, 10 mg. daily, for one week, and with vitamin B₁₂ intramuscularly, 30 μ g. daily, for ten days produced no response. (Fig. 5.) Because of similarities in erythrocytic morphologic

abnormalities and in bone marrow findings to those in CASE I, it was considered that this patient also might respond to oral crude liver extract.

His response to liquid extract of liver, U.S.P. (Valentine) in doses of 30 cc. three times daily for five weeks is shown in Figure 6. Reticulocyte response occurred reaching a peak of 7 per cent on the thirteenth day of therapy. The hematocrit rose from 28 to 43 per cent in two months. As with the first patient, relapse followed cessation of therapy. After five months, the hematocrit had fallen to 30 per cent. A rise and fall in the mean corpuscular hemoglobin concentration with response and relapse respectively were also observed.

On decreasing the dose of oral crude liver extract to 15 cc. three times daily, slight reticulocyte response occurred with a peak of 4 per cent on the thirteenth day of therapy; however, there was no subsequent rise in the hematocrit. On re-exhibition of the 30 cc. dose three times daily, response was again apparent with reticulocytosis and a rise in the hematocrit from 29 to 39 per cent in six weeks.

COMMENTS

These patients present a unique type of nutritional anemia, responding to a factor present in oral crude liver extract which previously has not been recognized as essential in human erythropoiesis. Although the mechanism of production of this anemia is unclear, some of the observed hematologic abnormalities may provide a basis for speculation on the nature of

possible metabolic aberrations in these patients. The combination of (1) hypochromia of erythrocytes, (2) erythroid hyperplasia with marked decrease in numbers of mature normoblasts in bone marrow, and (3) elevated serum iron levels with increased saturation of iron binding protein and hemosiderin deposition in tissues, suggests a failure of iron utilization in the synthesis of hemoglobin. Iron not utilized is then deposited in tissues as hemosiderin.

Of interest in this regard is a patient with "secondary hemochromatosis" terminating fatally reported by Goldish and Aufderheide.¹ In this patient a hypochromic anemia with erythrocytic morphologic abnormalities strikingly similar to those in our patients was present and was refractory to therapy with intramuscular vitamin B₁₂ and oral folic acid. As in our second patient, a history of alcoholism and laboratory evidence of impaired function of the liver were present. At autopsy, siderotic cirrhosis of the liver and hemosiderosis of other organs and tissues were found. There was no mention of the administration of crude liver extract to this patient.

Further, Gillman and Gillman² have described hemosiderin deposition and pigmentary cirrhosis in biopsy specimens of the liver obtained from adolescents and adults with pellagra. In their study, varying degrees of iron pigment deposition in the liver were found in eighty-two of ninety-two pellagrous subjects over ten years of age. Also, hypochromic and/or microcytic anemia have been described by others as a part of the syndrome of pellagra.^{3,4} However, hypochromic anemia has not been correlated with the presence of hemosiderosis in the same subject; contrarily, it has been attributed to lack of iron in a complex nutritional deficiency state. Nevertheless, these observations, along with the responses shown by our patients, might indicate an heretofore unrecognized factor in crude liver which is necessary for the synthesis of the hemoglobin molecule. In its absence, then, available iron might be deposited in tissues as hemosiderin and a hypochromic anemia might develop.

Hypochromic anemia, erythrocytic morphologic abnormalities with target cells, erythroid hyperplasia in bone marrow and hyperferricemia have also been observed in diet-induced pyridoxine deficiency in animals.⁵ A similar anemia resulting from pyridoxine deficiency has been produced experimentally in a pre-

mature infant.⁶ Furthermore, we recently reported an adult man with hypochromic anemia that responded only to pyridoxine.⁷ This patient was observed concomitantly with these presently reported. The clinical similarities were striking; the principle difference was his failure to respond to liquid extract of liver, U.S.P. (Valentine) in oral doses as large as 120 cc. daily. The response to pyridoxine in the presently reported cases has not yet been tested. It can be stated however, that active fractions obtained from the crude extract of liver have not contained pyridoxine by chromatographic and spectrophotometric analysis.⁸

Although to our knowledge the response of this type of anemia to oral crude liver extract has not been studied previously, a similar situation is suggested in the history of a patient recently reported by Kirketerp.⁹ This fifty-five year old woman is reported to have had severe iron-refractory hypochromic anemia that responded to an oral crude liver preparation, the folacin content of which was estimated as negligible. Details of bone marrow and erythrocytic morphology at that time are not available and the schedule of therapy is not included in the report. Twenty years later, a megaloblastic anemia which was refractory to refined liver extract but responded satisfactorily to folacin is described in this patient.

SUMMARY

1. Two patients are reported with an anemia, refractory to therapy with iron, vitamin B₁₂, folacin and leucovorin, that responded to the oral administration of liquid extract of liver, U.S.P. (Valentine).

2. The anemia was characterized by: (a) hypochromia and inconstant microcytosis, (b) erythrocytic morphologic abnormalities including anisocytosis, poikilocytosis and anisochromia; an increased number of target cells was prominent in one of the patients, (c) bone marrow hyperplasia with erythroid maturation arrest at an erythroblastic level, and (d) elevated serum iron levels with increased saturation of total serum iron binding capacity.

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Review

Agnogenic Myeloid Metaplasia*

Its Natural History and Present Day Management

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EXTRAMEDULLARY hemopoiesis or myeloid metaplasia due to unknown cause which is frequently associated with myelofibrosis or osteosclerosis is now a well recognized clinical and pathologic entity. In 1879, Heuck¹ described a patient with generalized osteosclerosis, anemia, leukocytosis and marked splenic and hepatic enlargement. Since Heuck's description the syndrome has been a controversial subject, the discussion revolving chiefly around the following questions: (1) Does it represent leukemia or a variant thereof? (2) Is it a compensatory mechanism secondary to a primary bone or bone marrow abnormality; such as, myelofibrosis and/or osteosclerosis? (3) Does it represent a reactive response to a marrow toxin or some other type of injury? (4) Is it a myeloproliferative disorder involving all marrow elements?

There are published case reports under a variety of names including chronic non-leukemic myelosis, aleukemic myelosis, leukoerythroblastic anemia, myeloid splenic anemia, leukanemia, osteosclerotic anemia, aleukemic megakaryocytic myelosis, atypical myeloid leukemia, primary idiopathic myelofibrosis and agnogenic myeloid metaplasia of the spleen. The last was first suggested by Jackson, Parker and Lemon² in their report of ten patients with extensive extramedullary hemopoiesis but without evidence of leukemia. Although numerous similarities to chronic granulocytic leukemia have been emphasized, there have also been many differences indicating that the disorder is a specific syndrome distinct from leukemia. The term agnogenic myeloid metaplasia has received fairly wide acceptance in recent years and will be used throughout the present discussion. The

frequent occurrence of fibrotic marrow changes appears to be a part of the overall disease process and, since the etiology remains unknown, the name agnogenic myeloid metaplasia seems quite inclusive and adequate at the present time in describing this condition and in setting it apart from extramedullary hemopoiesis secondary to some other primary disease.

With increasing awareness of the disorder and careful study and reporting of individual cases,³⁻¹⁹ certain diagnostic criteria have been established. The symptomatology has been rather nondescript and is often limited to complaints referable to anemia or to splenic enlargement of relatively long duration. However, in some cases migratory skeletal pain, especially in the lower extremities, is a prominent feature. Splenomegaly has been a constant finding and has usually been accompanied by hepatic enlargement. The absence of significant lymphadenopathy has been pointed out as an important aid in helping to differentiate agnogenic myeloid metaplasia from leukemia. The peripheral blood picture usually includes the presence of immature granulocytes and nucleated erythrocytes and therefore is described as compatible with a diagnosis of chronic granulocytic leukemia. The differential diagnosis rests upon the findings indicated plus the absence of leukemic marrow changes and, lastly and most important, the demonstration of active hemopoiesis in the spleen. The relatively chronic course of the disease has also been helpful in establishing this disorder as an entity separate from leukemia, although differentiation of the condition from leukemia has not received universal acceptance.¹⁴⁻¹⁸

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Early reports emphasized the poor response to antileukemic therapy. Both splenic radiation and splenectomy were formerly believed to be contraindicated. Hickling⁵ first called attention to the high mortality following splenectomy in agnogenic myeloid metaplasia. He described twenty-seven patients with twenty-four deaths in the twelve months following surgery, fifteen occurring within the first four weeks. It has, however, become increasingly evident that neither radiation nor splenectomy necessarily is followed by deleterious results and in certain carefully selected patients either may be the treatment of choice. Green, Conley, Ashburn and Peters²⁰ recently summarized the effect of splenectomy in twenty-nine patients and concluded that there was no evidence that it altered the general course of the disease. This conclusion has been substantiated by others.^{21,22}

The main histopathologic finding is that of active extramedullary hemogenesis without the changes commonly associated with leukemia. Areas of developing erythrocytes and granulocytes plus megakaryocytes are present in a slightly or markedly fibrosed spleen usually without infarcts. The lymphoid follicles are in most instances preserved and the splenic cords and sinusoids remain well demarcated. The latter may be somewhat distorted due to compression or distention but alteration of splenic architecture due to abnormal proliferation of a single marrow element so frequently seen in leukemia does not occur. In addition to those present in the spleen, there are occasional foci of hemopoiesis in other organs, the liver and abdominal lymph nodes following in that order of frequency. Whereas all normal marrow elements are involved in the proliferative process seen in agnogenic myeloid metaplasia, one or more cell types may be increased out of proportion to the others. Such a disturbance in normal cell ratios varies not only in different patients but in the several sites of extramedullary hemopoiesis which may be present in a single individual. This variability in proliferative activity undoubtedly accounts in part for differences in clinical manifestations. The normal hepatic architecture is usually not altered, and although it has been stated that there are no cellular infiltrates in the portal areas or vessel walls,¹⁸ others have reported hemopoiesis in the portal areas as well as in the sinusoids.¹⁷ When myelopoiesis is present in the nodes there is usually no definite structural derangement. Although considerably

less frequent in occurrence, myelopoiesis has been noted in the kidneys, lungs, adrenals, ovaries, and gastrointestinal tract.

The bone marrow findings have been reported as hypercellular, normal, hypocellular and, most commonly, fibrotic but without evidence of leukemia or proliferation of a single immature cell type. The last finding in a patient suspected of having leukemia should immediately suggest the possibility of myeloid metaplasia. The disparity between marrow aspirations and tissue biopsies and the importance of examining histologic sections in order to evaluate the status of marrow activity has been frequently stressed.^{17,18} Churg and Wachstein²³ reviewed the marrow findings in ninety-seven cases of leukemia and noted myelofibrosis of varying degrees without osteosclerosis in six patients with granulocytic leukemia. It was their conclusion that myelofibrosis is apparently not uncommonly associated with leukemia but osteosclerosis occurs very rarely if at all.

With respect to pathogenesis, Wyatt and Sommers¹⁸ reviewed reports of 129 cases in the literature and noted that nine authors regarded the disease as a form of leukemia, twenty-nine thought it was a reactive process but not neoplastic, and twelve others were undecided as to etiology. The differences between myeloid metaplasia and chronic granulocytic leukemia have been discussed and in our opinion the former should be considered a specific entity and not merely a variant of granulocytic leukemia.

Hemopoiesis in the lower vertebrates is exclusively extramedullary²⁴ and in the early developmental stages of the human embryo is a function of the connective tissue or mesenchyme. Erythrocytes are first formed in the blood islands of the yolk sac, followed by active hemopoiesis in the liver, spleen and lymph nodes. In human beings, intramedullary blood formation has its onset at about the fifth month of gestation and at the eighth month the marrow is the principal site of granulopoiesis and erythropoiesis. Splenic hemopoiesis gradually subsides and at birth functional extramedullary blood formation, except for lymphocytes and probably monocytes, no longer exists. The multipotential mesenchymal cells persist throughout life not only in bone marrow but in the spleen, liver, lymph nodes and elsewhere as a part of the reticuloendothelial system. These cells normally remain quiescent but they retain their embryonic

potentialities and under a variety of stimuli are capable of resuming active hemopoiesis. The spleen, therefore, is an important site of blood cell formation both in phylogenesis and ontogenesis.

Extramedullary hemopoiesis may occur in a wide variety of conditions and is especially common in children in association with anemia, infections, erythroblastosis foetalis and other conditions of increased demand.²⁵ In the adult it is seen in many diverse pathologic states such as leukemia, hereditary leptocytosis, myelophthitic anemias associated with metastatic neoplasm, pernicious anemia and hereditary spherocytosis.

It is possible to produce extramedullary myelopoiesis experimentally by a variety of methods¹⁷ including infection, hemolysins such as saponin and phenylhydrazine, marrow replacement and radiation. The myeloid metaplasia that results is similar histologically to the agnogenic type in man and the proliferation of a single cell type or the distortion of architecture characteristic of leukemia is not seen.²⁶ The experimental production of myelofibrosis by estrogens¹³ and the development of myeloid metaplasia in the adrenals and spleen following prolonged administration of anterior pituitary extracts²⁷ may have a bearing on the nature and etiology of agnogenic myeloid metaplasia. It should also be noted that *in vitro* cultures of bone marrow or leukocytes eventually lose their differentiation and become fibroblastic.

In 1908, Donhauser³ propounded the theory that in myelosclerosis the bone marrow was the primary site of the disease, leading to marrow failure with the development of extramedullary hemopoiesis as a compensatory mechanism. Myeloid metaplasia, however, does not always follow bone marrow failure. Notable examples of this are aplastic or hypoplastic anemias.²⁸ In these conditions extramedullary hemopoiesis rarely if ever develops. Myelofibrosis and osteosclerosis can occur in a number of conditions without myeloid metaplasia¹³ and the picture of a myelophthitic anemia is seen in only about 25 per cent of patients with Albers-Schönberg disease.²⁹ Vaughan and Harrison⁶ proposed, in 1939, that marrow sclerosis and leukoerythroblastic hyperplasia occur simultaneously in response to some unidentified stimulus with involvement of all cell types derived from the primitive mesenchymal reticulum cells of Maximow. They further suggested the possible close

relationship between polycythemia vera, megakaryocytic leukemia and what they termed myelosclerosis with leukoerythroblastic anemia, another designation for agnogenic myeloid metaplasia.

Tuberculosis or other chronic infection or exposure to bone marrow toxins have been considered of pathogenetic importance. Of the original ten cases described by Jackson et al. it was later reported³⁰ that six patients had a history of exposure to industrial solvents. Wyatt and Sommers¹⁸ in their analysis of thirty cases proposed that necrosis of partly matured bone marrow cells was the primary lesion followed by a reactive overgrowth of the surviving and usually more immature cells with the development of extramedullary hemopoiesis and proliferation of reticulum and stromal cells. They concluded that protracted bone marrow exposure to certain substances normally conjugated rapidly in the liver and excreted may be of considerable etiologic significance. They suggested five possible major groups of causative agents; namely, extrinsic toxins, liver dysfunction, endocrine disease, chronic hemorrhage or hemolysis and cardiovascular disease, and proposed that the protein breakdown products of partly mature hemopoietic cells serve as the stimulus to hyperplasia of the surviving cells and the development of extramedullary hemopoiesis. Peace¹⁹ also concluded that the process represents a mesenchymal reaction to injury and theorized that the common denominator of all benign myeloproliferative diseases may be the necrosis of immature hemopoietic cells. Dame-shke³¹ has emphasized the probable close relationship of myeloid metaplasia of the spleen to the myeloproliferative syndromes.

On the basis of current information, it appears more reasonable to consider the myelofibrosis or osteosclerosis which is usually present to be part of a proliferative disease involving both hemopoietic and stromal cells rather than a reaction to marrow failure with compensatory extramedullary hemopoiesis. This concept of a generalized myeloproliferative process allows for a considerably simplified classification of extramedullary hemopoiesis into two main categories: (1) primary, including agnogenic myeloid metaplasia with or without myelofibrosis or osteosclerosis and marrow sclerosis associated with neoplasm but without bone marrow metastases, and (2) secondary extramedullary hemopoiesis occurring with infections, leukemia, myeloph-

thisic anemias, hemolytic anemias, hereditary leptocytosis, and the like.

REVIEW OF CASES

Clinical Manifestations. In an attempt to define more clearly the clinical picture of this

TABLE I
AGE AT TIME OF DIAGNOSIS

Age (yr.)	Patients (no.)
37	1
40-49	8
50-59	14
60-69	23
70-79	9
80	1

interesting disorder we have reviewed all cases of agnogenic myeloid metaplasia diagnosed at University of Michigan Hospital through June, 1955. Fifty-six patients have been so classified in the past thirteen years. Prior to the early 1940's cases were coded under a variety of diagnoses

TABLE II
SYMPTOMS PRESENT IN FIFTY-SIX PATIENTS AT TIME OF DIAGNOSIS

Symptoms	Minimal	Moderate	Severe	Absent	No Record
Weakness	22	22	5	7	0
Pressure symptoms secondary to splenomegaly	21	14	7	14	0
Weight loss	16	13	13	13	1
Dyspnea	16	6	1	33	0
Night sweats	14	6	1	32	3
Bone pain	8	7	4	37	0
Bleeding	11	2	4	38	1
Fever	8	2	0	44	2
Hypermetabolism	6	3	0	41	6

and have not been included in this series, although the presence of myeloid metaplasia appeared quite evident in many instances.

Our series consists of twenty-nine men and twenty-seven women. All were Caucasian. The age at the time of diagnosis ranged from thirty-seven to eighty years with a median of 62.5 and an average of 60.4 years. (Table I.) Their occupations were varied. There are twenty-four patients still alive, seventeen are dead and the present status of fifteen is unknown.

The duration of symptoms at the time of diagnosis varied from two to two hundred four

months with an average of thirty-seven months. The initial complaint was weakness or ease of fatigue in twenty-nine patients, pressure from or knowledge of an enlarged spleen in fourteen, bone pain in five, weight loss in two, abnormal bleeding in one, dyspnea in one, night sweats in

TABLE III
PHYSICAL FINDINGS IN FIFTY-SIX PATIENTS AT TIME OF DIAGNOSIS

Physical Findings	Present	Absent	No Record
Splenomegaly	55*	1†	0
Hepatomegaly	50	6	0
Peripheral edema	15	41	0
Cardiomegaly	14	42	0
Petechiae or purpura	9	47	0
Bone tenderness	6	49	1
Enlargement of nodes	3	53	0
Jaundice	3	53	0
Ascites	2	54	0

* Three patients were postsplenectomy with reported splenomegaly prior to surgery.

† Although the spleen was not palpable, enlargement was demonstrated by x-ray.

one and three were asymptomatic, splenomegaly having been discovered during a periodic health examination. Symptoms present at the time of diagnosis and the degrees of their severity are shown in Table II.

The significant physical abnormalities found on the initial examination are listed in Table III. The patient without palpable splenic enlargement had evidence of an enlarged spleen on roentgenogram. Three patients had reported splenomegaly before splenectomy, performed prior to our initial examination. In twenty-one of the fifty-three patients in whom the spleen was retained, the organ was palpable 5 to 10 cm. below the left costal margin, 10 to 15 cm. in fourteen, 15 to 20 cm. in four, over 20 cm. in ten and less than 5 cm. in only three. The hepatic enlargement was greater than 10 cm. below the right costal margin in only seven instances. Of the three patients with significant enlargement of the peripheral nodes, one had slight and one moderate generalized adenopathy and one had only enlarged inguinal nodes. Only two patients were noted to be emaciated or cachectic, seventeen were undernourished, thirty well nourished and seven were obese.

Significant associated diagnoses are shown in Table IV. It is of interest that none of these fifty-six patients had tuberculosis, only two had neoplasms (in both instances carcinoma of the prostate) and five (8.9 per cent) had a previous diagnosis of polycythemia vera. Review of the

TABLE IV
ASSOCIATED PRESENT OR PRIOR DIAGNOSES

None	38
Cholelithiasis and/or cholecystitis	6
Polycythemia vera	5
Diabetes mellitus	3
Carcinoma (prostate)	2
Organic heart disease	2
Gout	1
Syphilis	1

family histories of these patients yielded little information. In eight patients there was a family history of a blood disorder including one instance of leukemia and one of anemia and an enlarged spleen.

In view of the possible role of bone marrow toxins, such as industrial solvents, in the development of agnogenic myeloid metaplasia, special attention was paid to this point. In some instances the records were not sufficiently informative to exclude contact with such agents but in any event there was a history of questionable slight exposure in only five patients. Perhaps of some interest is the fact that one patient, when a young man, had been employed for several years as an x-ray technician.

Laboratory Findings. The peripheral blood findings at the time of diagnosis are summarized in Table V. The majority of the patients had moderate or severe anemia, which was usually normocytic and normochromic. The leukocyte count was extremely variable, higher than normal values prevailing. We have not observed leukocyte counts above 82,750 per cu. mm. at any time during the course of the disease. There were only eight patients without immature granulocytes in the peripheral blood and thirty-four had either myeloblasts or progranulocytes or both. Eight patients demonstrated eosinophilia, six an increase in basophils and seven monocytosis. Heavy toxic granulation of the neutrophils was noted in seven. There were abnormal monocytes in eight, abnormal lymphocytes in three, plasmocytes in three and hemohistiocytes were recorded in the peripheral blood of ten patients.

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TABLE V
SUMMARY OF PERIPHERAL BLOOD FINDINGS IN
FIFTY-SIX PATIENTS

Blood Findings	No. of Patients
Hemoglobin (gm. %)	
5-6.9	8
7-8.9	13
9-10.9	15
11-12.9	17
13-14	3
Range 5-14	
Average 9.7	
Mean corpuscular volume (cu. microns)	
Normal	34
Microcytic	12
Macrocytic	9
Unknown	1
Range 71-103	
Average 88	
Mean corpuscular hemoglobin concentration (%)	
Normal (30-36)	41
25-29	13
20-24	2
White blood count (per cu. mm.)	
Normal (4,000-10,000)	20
Leukopenia	6
Leukocytosis	30
Range 1,200-45,800	
Average 12,900	
Myeloblasts and/or progranulocytes	34
Range 0-2,790 per cu. mm.	
Average 395 per cu. mm.	
Myelocytes and/or metamyelocytes	48
Range 0-9,746 per cu. mm.	
Average 1,440 per cu. mm.	
Band and segmented neutrophils	56
Range 516-38,930 per cu. mm.	
Average 8,169 per cu. mm.	
Anisocytosis and poikilocytosis	
Absent	0
Slight	2
Moderate	24
Marked	30
Nucleated erythrocytes (per 100 white blood cells)	
Absent	15
Present	41
1 to 4	27
5 to 9	11
10 or more	3
Platelets	
Decreased:	
Markedly	2
Moderately	4
Slightly	7
Normal	13
Increased:	
Slightly	5
Moderately	14
Markedly	11

Poikilocytosis characterized by numerous elongated, teardrop and comma forms, and accompanied by appreciable anisocytosis, are findings of considerable diagnostic importance in agnogenic myeloid metaplasia and have not received the attention in the literature which

TABLE VI
TYPES OF THERAPY AND NUMBER OF CASES
IN WHICH EMPLOYED

Therapy	Prior to Diagnosis of Agnogenic Myeloid Metaplasia	For Agnogenic Myeloid Metaplasia
Transfusions only.....	..	21
Corticosteroids.....	..	8
Splenic radiation.....	7	7
Splenectomy.....	3	..
Radioactive phosphorus...	..	3
Fowler's solution.....	2	..
Nitrogen mustard.....	..	2
Triethylene melamine....	..	1
Urethane.....	1	..
No treatment to date.....	..	6
Unknown.....	..	10

they deserve. These red cell changes were present in every instance. Nucleated erythrocytes were noted in the peripheral blood in the majority of the patients. Although usually found in small numbers, one patient reached a level of over 1,000 nucleated erythrocytes per 100 leukocytes. The reticulocyte count was less than 3 per cent in sixteen patients, between 3 and 10 per cent in thirty-seven and above 10 per cent in three. Red cell fragility tests were not done in a sufficient number of instances to be of any import, although decreased resistance to hypotonic salt solution was noted in two patients with superimposed hemolysis.

The platelets presented distinct abnormalities. Although there are numerous reports of thrombocytopenia accompanying agnogenic myeloid metaplasia, in our series thrombocytosis was more commonly encountered. Furthermore, the platelets were large and of bizarre appearance in nearly every instance.

Specimens obtained by bone marrow aspiration were hypocellular in fifty-two of the fifty-six patients. In the remainder there was either normal or increased cellularity, but in only two instances was there a distinct relative and abso-

lute increase in granulocytic elements such as characterizes chronic granulocytic leukemia. In many patients there were large masses of platelets in the bone marrow aspirate without a proportional increase in megakaryocytes. Bone marrow trephines or biopsies were performed on fifteen patients and the specimens were hypocellular in twelve, usually with increased marrow fibrosis.

Splenic cytologic material had been obtained in thirty-six patients; by needle aspiration in thirty-two, by laparotomy with biopsy in one and by splenectomy in three. Myelopoiesis was demonstrated in all but one instance. Although splenic cytology in this patient appeared to be essentially normal, all other findings as well as the subsequent course have been compatible with the diagnosis of myeloid metaplasia. Biopsies of the liver were performed on three patients, with demonstration of active hemopoiesis in two. Biopsies of lymph nodes were carried out in two patients and one of these specimens showed extramedullary myelopoiesis.

Roentgenographic skeletal surveys were carried out in thirty-two patients and in eight increased bone density was demonstrated. The total serum bilirubin was below 0.5 mg. per cent in twenty-two of forty-seven patients in whom the values were obtained, between 0.5 and 1.0 mg. per cent in seventeen, 1.0 and 2 mg. per cent in six, and over 2 mg. per cent in two. In one patient there was an increase above 5 mg. per cent. Urine urobilinogen was determined in thirty patients and was normal in twenty, slightly elevated in nine and slightly decreased in one. Plasma protein levels were determined in nineteen patients and were normal in seven. The plasma globulin was elevated in four, and there was decreased albumin with normal globulin in seven. In one the total was reduced but fractionation was not done. Other blood chemistry values such as serum calcium, phosphorus and alkaline phosphatase were not obtained in a sufficient number of patients to be of significance. Tests for incomplete antibodies, including direct and indirect Coombs' tests, were negative in the twenty-three patients on whom these procedures were performed.

Treatment. The treatment of the fifty-six patients with agnogenic myeloid metaplasia has varied considerably. The number of instances and types of treatment employed are shown in Table VI, and the results of treatment in Table VII. It is, of course, difficult to evaluate the effects

of therapy in a group of patients presenting such diverse symptoms and signs. An effort was made to determine the major cause of disability in each patient. The findings are listed in Table VIII. It can be seen that in the symptomatic patients, anemia and massive splenomegaly were the

TABLE VII
RESULTS OF TREATMENT

No significant change	8
Marked improvement	1
Moderate improvement	4
Slight improvement	3
Condition worsened	3
No treatment to date	6
No record or unknown	10
Transfusions only, with symptomatic improvement . . .	21

TABLE VIII
MAJOR CAUSE OF DISABILITY

Progressive anemia	20
Pressure symptoms secondary to splenomegaly	14
Hypersplenism (hemolysis)	4
Abnormal bleeding	2
Bone pain	1
Unknown	2
No symptoms attributable to myeloid metaplasia . .	13

chief causes of disability. Early in the disease no treatment is indicated and in many instances the only therapy beneficial throughout the illness is transfusions. Although the number of patients is small, the best therapeutic results were obtained in the group with superimposed hemolysis who were treated with corticosteroids.

Prognosis. Of the fifty-six patients, twenty-four are still alive and under observation; the present status of fifteen is unknown. Seventeen patients are dead, with available necropsy reports in six. In all instances necropsy findings confirmed the diagnosis of agnogenic myeloid metaplasia. The total duration of the disease in the group followed up to termination ranged from twelve to two hundred eight months with an average of seventy-two months. These patients were followed up from three to one hundred twelve months after the diagnosis was made. The patients still being followed up have had the disease from twelve to one hundred twenty-one months and have been observed from three to one hundred twelve months. A considerable variation in the duration of the disease is evident and in one female patient asymptomatic splenomegaly was known to have

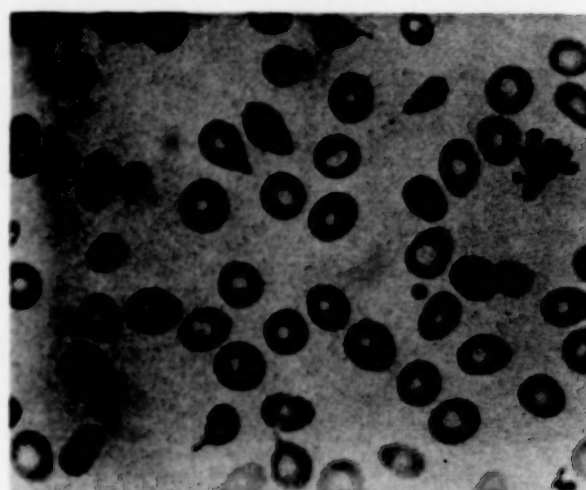


FIG. 1. Blood film of the patient described in Case 1 illustrating the variation in size and shape of the erythrocytes; original magnification, $\times 1,400$.

been present for seventeen years before the diagnosis of myeloid metaplasia of the spleen was made. In occasional instances the correct diagnosis was suggested only by the subsequent course of the disease following a prior diagnosis of early chronic granulocytic leukemia. Re-evaluation of the patient then substantiated the impression that the initial diagnosis was in error.

CASE REPORTS

The following cases were selected to be described in detail as illustrative of the rather diverse clinical manifestations of agnogenic myeloid metaplasia.

CASE 1. T. H., No. 537603, a forty-seven year old male research engineer, was first seen in December, 1943. He complained of pallor that had been present for fifteen years, recurrent pain in the left hip for six to eight years, left upper abdominal pain which was aggravated by coughing, deep breathing and exertion for one year, and ease of fatigue which had been especially severe for four months. Physical examination demonstrated pallor, minimal cardiomegaly, spleen palpable 10 cm. below the left costal margin, and liver edge 3 cm. below the right costal margin. The hemoglobin was 8.9 gm. per cent, red blood cell count 3.4 million, hematocrit 28.5 and white blood cell count 4,300. The differential revealed myelocytes 5, metamyelocytes 25, band neutrophils 22, segmented neutrophils 15, prolymphocytes 2, lymphocytes 26 and monocytes 5 per cent. There was moderate poikilocytosis and anisocytosis (Fig. 1), 2 nucleated erythrocytes per 100 leukocytes and moderate thrombocytosis. Sternal aspiration yielded a hypocellular specimen which consisted chiefly of small basophilic metarubricytes with many megakaryocytic nuclei. Splenic aspirate was cellular with all normal marrow elements

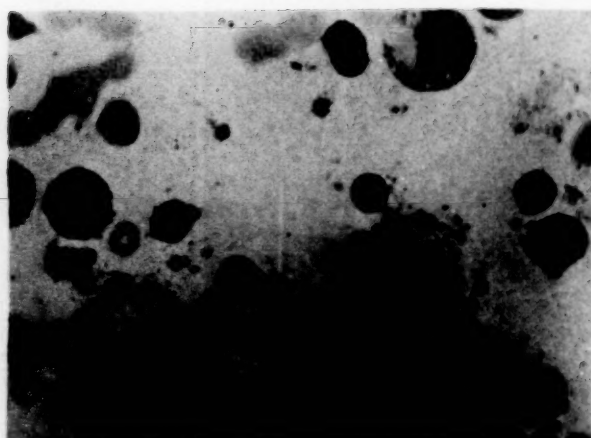


FIG. 2. Material obtained by splenic aspiration in Case I demonstrating active erythropoiesis, granulopoiesis and thrombopoiesis; original magnification, $\times 1,400$.

present. (Fig. 2.) Bone x-rays demonstrated generalized osteoporosis with distinct coarsening of the trabecular pattern of the spine, pelvis, upper femora, scapulas, humeri and ribs. Treatment with ferrous sulfate, vitamin D and calcium was instituted. The patient's symptoms and physical and laboratory findings remained essentially unchanged throughout the following three years and he received his first blood transfusion in February, 1947. A sternal marrow biopsy specimen in November, 1946, showed practically no cellular marrow with an increase in bone and an abnormal pattern of closely compacted bony trabeculae with very small marrow spaces. Following his first transfusion in February, 1947, the patient continued essentially in *status quo* until August, 1948, when his hemoglobin was 5.6 gm. per cent, white blood cell count 4,900 and blood film unchanged over the initial examination except for the presence of a small number of myeloblasts. At this time his spleen was felt 12 cm. below the left costal margin and the liver 11 cm. below the right costal margin. A number of liver function studies were normal as were serum calcium, phosphorus and alkaline phosphatase levels. Bone x-rays were unchanged. He received a single transfusion at two to six month intervals until early 1951 when about five transfusions per month became necessary to maintain tolerable erythroid values. In the interim he had been treated with folic acid, vitamin B₁₂ and cobaltous chloride without improvement. By June, 1951, his spleen had enlarged considerably and he complained of increasingly severe bone pain. Repeat marrow and splenic aspirations were essentially unchanged over the findings of eight years before. The serum bilirubin was 0.4 mg. per cent. Cortisone therapy was instituted in doses of 300 mg. per day. The only noticeable effect of this drug was a slight reduction in the size of the spleen. The dosage was decreased after two weeks to 75 mg. per day and discontinued two weeks later. Subsequently his erythroid values fell. Cortisone therapy

was reinstituted and he was given 600 r over the spleen during a ten-day period. Following radiation the spleen decreased considerably in size. The patient was then maintained on frequent transfusions and cortisone 75 mg. per day. He continued on this program with transfusions at about weekly intervals and was able to resume work. He was last seen in May, 1952, at which time his spleen was palpable 17 cm. below the left costal margin and the white count was 19,450 with progranulocytes 6, myelocytes 14, metamyelocytes 16, band neutrophils 34, segmented neutrophils 11, lymphocytes 2, monocytes 12 and basophils 5 per cent. The patient continued to require frequent transfusions and died in April, 1953, at another hospital.

Comment. This patient presents the typical clinical picture and course of agnogenic myeloid metaplasia with its late period characterized by progressive anemia and massive splenomegaly. Myelofibrosis and myelosclerosis were demonstrated and bone x-rays were abnormal. He was treated with both corticosteroids and splenic radiation without significant improvement. At no time was there evidence of hemolysis, although red cell survival studies were not performed. The total duration of his symptoms was approximately seventeen years.

CASE II. S. E., No. 519178, a fifty-three year old male clothier, was first seen in January, 1951. Three years earlier splenomegaly had been noted on a routine physical examination. In late 1949, abnormal cells were first seen in the peripheral blood. The patient remained entirely asymptomatic, although his spleen progressively increased in size, until October, 1950, when he began to experience weakness, exertional dyspnea, weight loss, afternoon fever and intermittent night sweats. He received fourteen transfusions between October, 1950 and January, 1951. Three weeks after a blood transfusion physical examination revealed pallor, icteric scleras, splenomegaly extending 16 cm. below the left costal margin and 3 cm. to the right of the midline, and a liver edge 4 cm. below the right costal margin. The hemoglobin was 7.3 gm. per cent, red blood cell count 2.5 million, hematocrit 23 and white blood cell count 12,600. The differential count was myelocytes 2, progranulocytes 2, myelocytes 3, metamyelocytes 7, neutrophils 75, lymphocytes 8 and monocytes 3 per cent with 8 nucleated erythrocytes per 100 leukocytes. The reticulocytes were 8 per cent. Rare spherocytes were noted on the blood film and the platelets were present in normal numbers but were large and bizarre. There was marked variation in the size and shape of the red cells. The serum bilirubin was 1.0 mg. per cent with 0.1 mg. per cent as sodium bilirubinate. The urine urobilinogen was normal. Cold agglutinins were demonstrable in a 1:1 titer. Sternal aspiration yielded a somewhat hypocellular specimen with a relative decrease in early granulocytic forms and abnormal erythropoiesis with bizarre micrometarubricytes. Rare

megakaryocytes were seen. Sternal trephine revealed essentially the same picture but with more immature granulocytic and erythrocytic elements. Splenic aspiration demonstrated active hemopoiesis. Bone x-rays revealed spotty demineralization of the femoral heads. The red cells showed decreased resistance to hypotonic salt solution.

The patient was given a transfusion of 1,000 ml. of whole blood and started on oral cortisone 300 mg. per day. After fourteen days the dosage was reduced to 50 mg. per day. On the larger doses of cortisone his hemoglobin increased approximately 2 gm. per cent and his spleen decreased moderately in size. Cortisone was maintained in doses of 50 to 75 mg. per day throughout life. The patient required no transfusions from February, 1951, until August, 1952, although sixteen transfusions during the four months preceding cortisone therapy had been unsuccessful in maintaining satisfactory erythroid values. Throughout this eighteen month period his hemoglobin remained between 10 and 11 gm. per cent, the other peripheral blood findings were unchanged, and the patient was essentially asymptomatic. In late August, 1952, fever developed, there was a cough with purulent sputum and the patient became stuporous and disoriented. In spite of massive antibiotic therapy his course was progressively downhill and he died on September 2, 1952.

Necropsy revealed an acute fibrinopurulent lobular pneumonia. Advanced myelofibrosis was present with large primitive reticulum cells. There was active hemopoiesis in the spleen, liver and lymph nodes. The spleen weighed 3,300 gm. and showed nearly complete loss of the follicles with active granulopoiesis and erythropoiesis and numerous megakaryocytes. Some retroperitoneal nodes demonstrated numerous large primitive mononuclear cells with a neoplastic appearance.

Comment. This case illustrates the clinical picture of agnogenic myeloid metaplasia with superimposed hemolysis. The latter was well controlled with maintenance cortisone therapy in small doses until the terminal acute pneumonia. The necropsy findings, although not typical of leukemia, are very suggestive of a neoplastic process and would seem compatible with the concept that agnogenic myeloid metaplasia is a myeloproliferative disorder with certain distinct characteristics.

CASE III. O. DEP., No. 268957, a fifty-two year old male violinist, was first seen in January, 1948. Two years earlier a diagnosis of gastric ulcer was made and he responded well to treatment. In June, 1946, he noted a left upper abdominal mass and the onset of weight loss, weakness and ease of fatigue. These symptoms gradually increased in severity. He denied jaundice but had noted intermittently dark urine. He had never had a transfusion. On his initial examination the spleen extended 11 cm. below the left costal margin. The liver was not palpable

and the remainder of the physical examination was non-contributory.

The hemoglobin was 8.1 gm. per cent, red blood cell count 2.6 million, hematocrit 25 and white blood cell count 9,600. The differential revealed myeloblasts 1, progranulocytes 1, myelocytes 1, metamyelocytes 4, band neutrophils 16, segmented neutrophils 63, lymphocytes 3, monocytes 3, basophils 7 and plasmocytes 1 per cent. There was extreme variation in the shape and size of the red cells and spherocytes were present. The platelets were moderately increased in number and were large and bizarre. Two nucleated red cells per 100 white cells were seen and the reticulocytes were 10 per cent. The red cells showed increased fragility in hypotonic salt solution. The serum bilirubin was 0.61 mg. per cent. Sternal aspiration revealed a diffusely cellular marrow with active myelopoiesis but nothing to suggest a leukemic process. Splenic aspiration demonstrated active hemopoiesis.

The patient received periodic transfusions and remained in fair health until August, 1949, when he was rehospitalized complaining of an increasing need for transfusions. He was slightly icteric and the physical examination was otherwise unchanged except for a liver edge palpable 7 cm. below the right costal margin. The peripheral blood findings were essentially those recorded at the time of diagnosis. The serum bilirubin was 1.3 mg. per cent with 1.2 mg. per cent in the indirect or bilirubinglobin form. An attempted sternal aspiration was unsuccessful but sternal trephine gave a specimen with a gross fibrotic appearance which was quite hypocellular. Megakaryocytes were present. The patient was maintained on increasingly frequent transfusions until June, 1951, when he was given splenic radiation and started on a regimen of cortisone which was continued in a dosage of 50 mg. daily throughout the remainder of life. On this program the size of the spleen decreased and there was a sharp reduction in his transfusion requirements. He continued in relative comfort until December, 1952, when he died in another hospital with a reactivated peptic ulcer and acute terminal pneumonia.

Comment. This patient, as the patient in Case II, had hemolysis as the major manifestation of his disease. Although he was given splenic radiation at the same time the cortisone therapy was started the persistent improvement over the next eighteen months would point to cortisone as the responsible therapeutic agent. Another patient with agnogenic myeloid metaplasia and superimposed hemolysis (W. L. No. 706297) has now been maintained on cortisone 50 mg. per day for four years without transfusions or other therapy. He has remained active and relatively free of symptoms.

CASE IV. W. O., No. 726478, a fifty-nine year old male furniture salesman, noted the onset of pain in the lower part of his back in November, 1951. One month later he experienced pain in both tibias,

knees, ankles and hips with slight fever and exertional dyspnea. He was found to be anemic and received six transfusions prior to his first examination by us in April, 1952.

Bone pain remained as his chief complaint. Physical examination revealed the spleen and liver edges to be palpable 5 and 4 cm. below the left and right costal margins respectively and moderate pitting edema of the lower extremities. The hemoglobin was 11.4 gm. per cent (his last transfusion was three weeks before this examination), red blood cell count 3.9 million, hematocrit 39 and white blood cell count 7,200. There were myelocytes 2, metamyelocytes 1, band neutrophils 2, segmented neutrophils 62, lymphocytes 24, monocytes 8 and eosinophils 1 per cent. One nucleated erythrocyte was seen per 100 leukocytes and red cells demonstrated extreme anisocytosis and poikilocytosis. The platelets were 226,200 per cu. mm. and the reticulocytes were 4.2 per cent. Certain liver function studies were normal. The alkaline and acid phosphatase levels of the serum were 56.0 and 1.2 King-Armstrong units respectively. Serum calcium and inorganic phosphorus values were 8.8 and 2.4 mg. per cent. Bone x-rays showed increased density in all visible bones with a tendency toward obliteration of the medullary canals and thickening of the cortex. These findings were not present on previous roentgenograms obtained in January, 1952.

Both sternal aspiration and trephine biopsy specimens were obtained and revealed very dense bone with striking hypocellularity. Splenic aspiration demonstrated active hemopoiesis with all types of developing myeloid cells.

Only symptomatic treatment was advised and the patient died at another hospital in late October, 1952, about one year after the onset of symptoms. Autopsy revealed carcinoma of the prostate with extension to the pelvic organs and metastases to the retroperitoneal nodes, left adrenal gland and dura mater. There was extensive sclerosis of the bone marrow.

Comment. Although the clinical and laboratory findings were entirely compatible with agnogenic myeloid metaplasia, the patient died with a carcinoma of the prostate. Metastases were present elsewhere but there was no evidence of metastases to bone marrow either at the time of diagnosis or at autopsy eight months later. Advanced sclerosis of the marrow cavity was present, and the case appears to be an example of myeloid metaplasia associated with neoplasm and osteosclerosis, but without involvement of the marrow by the neoplastic process itself. Since the findings were not those of myelophthisic anemia associated with metastatic bone marrow involvement, it seems justifiable to include this case in the myeloid metaplasia series. The association between the malignancy and the extramedullary hemopoiesis cannot be clearly defined and the coincidental occurrence of disseminated carcinoma in a patient with otherwise "typical" agnogenic myeloid metaplasia must be con-

sidered. The bone changes apparent on roentgen films were generalized and were interpreted as osteosclerosis and not metastases to the bone. The only other patient in our series with recognized associated neoplasm also has a carcinoma of the prostate. He is still alive and has not demonstrated the bone abnormalities on x-ray seen in the patient described above.

CASE V. L. B., No. 342132, was a fifty year old male laborer in whom the diagnosis of myeloid metaplasia was made in July, 1950. He was first seen at University Hospital in 1934 and again in 1944 for treatment of syphilis of the central nervous system. His hemogram on the latter date was entirely normal. He was not seen again until July, 1950, when he returned complaining of weakness and ease of fatigue during the preceding eighteen months and a progressive increase in the size of his abdomen with a left upper abdominal mass of twelve months' duration. Physical examination revealed an undernourished white man with primary optic atrophy and Argyll Robertson pupils, and slight cardiomegaly. The spleen extended 7.5 cm. and the liver 13 cm. below the left and right costal margins, respectively.

The hemoglobin was 9.0 gm. per cent, red blood cell count 3.8 million, hematocrit 28 and white blood cell count 44,300. All "leukocyte" hemocytometer counts were corrected for the number of nucleated erythrocytes. The differential revealed myelocytes 18, metamyelocytes 4, band neutrophils 3, segmented neutrophils 30, eosinophils 15, lymphocytes 18 and monocytes 12 per cent. There was severe toxic granulation of the neutrophils. Anisocytosis, poikilocytosis and 246 nucleated erythrocytes per 100 white cells were observed. The Kahn serologic reaction was negative. The serum bilirubin was 0.7 mg. per cent, gamma globulin 43 units, bromsulphalein test 9 per cent retention of dye at the end of forty-five minutes, and the total serum proteins were 8.2 gm. per cent with 3.4 gm. per cent albumin and 4.8 gm. per cent globulin. Roentgenographic skeletal survey was negative.

Sternal aspiration yielded a diffusely cellular specimen without clumps. The erythroid:granulocyte ratio was 1:1 and all stages of erythropoiesis were represented with rubricytes and metarubricytes predominating. Granulopoiesis was without maturation defect. Splenic aspiration demonstrated chiefly splenic lymphocytes. Fibroblasts and fibrocytes were present, plus a few metarubricytes, but the aspirated material was not considered diagnostic of myeloid metaplasia. Surgical biopsies of the liver and spleen were performed with the latter showing active hemopoiesis without evidence of neoplasm. Increased numbers of granulocytes were noted in the liver sinusoids and portal canals. An omental lymph node showed only a somewhat atypical hyperplasia.

The patient was given a transfusion. His clinical status and findings remained essentially unchanged. In July, 1951, his white count was 62,880 and there

were 259 metarubricytes and 6 rubricytes per 100 leukocytes in the peripheral blood. The differential count was as before but the platelets had dropped to 90,000, and they were large and atypical in appearance. The reticulocytes were 7.1 per cent. Direct and indirect Coombs' tests were negative and incomplete antibodies could not be demonstrated by other methods. Treatment was begun with cortisone 300 mg. daily. His hemoglobin increased from 11 to 13.5 gm. per cent, platelets from 72,000 to 179,400 and his white count fell from 74,700 to 31,870. After fifteen days, cortisone was reduced to 75 mg. per day and continued until February, 1952, when it was stopped because of a pyogenic pulmonary infection. At that time his white count was 29,920 and there were 1,063 nucleated erythrocytes per 100 leukocytes in the peripheral blood. The patient failed to return and he died elsewhere in February, 1954. The circumstances surrounding his death and the clinical course in the intervening two years are unknown.

Comment. Although the follow-up in this patient is incomplete, his case is described in some detail because of the markedly disturbed erythropoiesis, the peripheral blood nucleated erythrocyte count far exceeding the leukocyte count. At no time could a diagnosis of leukemia be established. The erythrocytic findings in this patient apparently represent a variant of a generalized myeloproliferative process with altered erythropoiesis as a dominant feature.

CASE VI. O. L., No. 414790, was a male pharmacist who was first seen in 1937 at the age of thirty-seven when a diagnosis of polycythemia vera was made. The red count was 6.04 million, hemoglobin 18.0 gm. per cent, and white count 28,600. The platelets were slightly increased in number and were large. His spleen was palpable 4 cm. below the left costal margin. No treatment was advised and he was not seen again for ten years when he reported that except for some decrease in his general strength he had been essentially well. He had, however, noted some increase in the size of his spleen. He had never received treatment for polycythemia vera. The spleen at that time was palpable 4 cm. below the umbilicus and 1 cm. to the right of the midline, and the liver edge descended 4 cm. The hemoglobin was 13.1 gm. per cent, red blood cell count 4.7 million, hematocrit 41 and white blood cell count 24,300. There was extreme poikilocytosis, the platelets were large and moderately increased in number and the differential count revealed myelocytes 2, metamyelocytes 4, band neutrophils 31, segmented neutrophils 54, lymphocytes 4, eosinophils 1 and basophils 4 per cent.

Sternal aspiration produced a hypocellular specimen with few megakaryocytes but many large clumps of platelets. Splenic aspiration demonstrated active granulopoiesis and erythropoiesis plus large numbers of platelets with some megakaryocytic nuclei and fragments.

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No treatment was advised and when next examined in December, 1948, he had continued asymptomatic and the physical and laboratory findings were essentially unchanged except for scleral icterus, a moderate reticulocytosis and a serum bilirubin of 2.6 mg. per cent.

The patient was not seen again until February, 1955 (six years later). He had continued to work daily but for two to three years had noted exertional dyspnea and ankle edema and for three months had been aware of progressive enlargement of his spleen with discomfort in the left side of the abdomen. He had had no blood counts, transfusions or other therapy since his last examination in 1948. He was thin and pale and had icteric scleras, moderate pitting edema of both lower extremities, and the spleen was palpable 25 cm. below the left costal margin and extended 5 cm. to the right of the midline. The liver was not palpable.

His hemoglobin then was 4.4 gm. per cent, red blood cell count 2 million, hematocrit 19 and white blood cell count 16,300. The differential count showed myeloblasts 3, progranulocytes 2, myelocytes 6, metamyelocytes 3, band neutrophils 14, segmented neutrophils 50, lymphocytes 10, monocytes 4, eosinophils 3 and basophils 5 per cent. The platelets were slightly increased in number, the reticulocytes were 5 per cent and there was striking variation in the size and shape of the erythrocytes. The serum bilirubin was 1.7 mg. per cent with 1.6 mg. per cent in the indirect fraction. Direct and indirect Coombs' tests were negative and incomplete antibodies were not otherwise demonstrated.

Hospitalization for transfusions and the institution of corticosteroid therapy was advised but the patient refused. He was next seen in October, 1955, when he stated that following his last examination he had started to take cortisone in a dosage of 75 mg. per day. He noted symptomatic improvement and there was a reported increase in his erythroid values. After two months symptoms developed apparently due to electrolyte imbalance and fluid retention and he discontinued the cortisone, with return of weakness, anorexia and weight loss. Physical examination and the peripheral blood findings in October, 1955, were essentially unchanged over those present eight months before. The serum bilirubin was 2.0 mg. per cent with 1.7 mg. per cent in the indirect fraction. The fecal urobilinogen excretion was 472 mg. per twenty-four hours. Decreased red cell survival was demonstrated by the radioactive chromium technic.

The patient refused any medication other than blood transfusions and left the hospital against advice.

Comment. This case is described as an instance of agnogenic myeloid metaplasia evolving from polycythemia vera, a transition which has been frequently mentioned in the literature. The case also illustrates the lengthy course so often seen in myeloid metaplasia

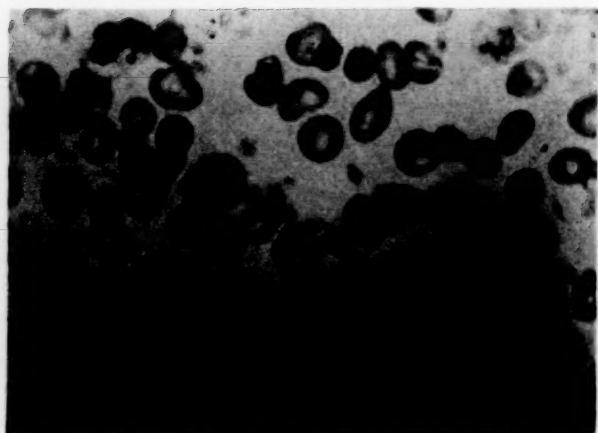


FIG. 3. Case VII. Brilliant cresyl blue blood film counterstained with Wright's stain. Note the increase in thrombocytes, their large size and bizarre appearance; original magnification, $\times 1,400$.

during which the patient requires no treatment and remains essentially without symptoms. It has been stated that in 10 to 20 per cent of patients with polycythemia vera myeloid metaplasia³¹ will eventually develop. The patient just described is one of five patients in our series of fifty-six who had a previous diagnosis of polycythemia vera.

CASE VII. J. S., No. 804663, a sixty-four year old housewife, was seen initially in February, 1955. She had had known hypertension for seventeen years and ten years ago noted the onset of intermittent left upper abdominal pain. Roentgen examination at this time is reported to have shown splenic enlargement but blood studies were not done. In early 1953, the spleen was palpable and anemia was found. The patient was given 500 ml. of whole blood and her spleen was removed at another hospital in February, 1953. She was asymptomatic following splenectomy until June, 1954, when she fell and fractured the transverse process of L5. Subsequently pedal edema and albuminuria developed and she was referred to University Hospital for evaluation. She reported a 20 pound weight loss over the past year and minimal tiredness and ease of fatigue since June, 1954. Her blood pressure was 210/100, there was a grade II hypertensive retinopathy, a moderate degree of pretibial edema, and the liver was felt 8 cm. below the right costal margin.

The hemoglobin was 10.4 gm. per cent, red blood cell count 3.4 million, hematocrit 34 and white blood cell count 25,250. The differential count showed myelocytes 1, metamyelocytes 1, band neutrophils 16, segmented neutrophils 52, lymphocytes 24 and eosinophils 6 per cent. Platelets were tremendously increased in number and were large and bizarre in appearance. (Fig. 3.) There was an unusual degree of anisocytosis and poikilocytosis. The reticulocytes were 1.2 per cent

and there were 2 nucleated red cells per 100 leukocytes. The serum bilirubin was 0.2 mg. per cent and the total serum proteins were 5.4 gm. per cent with 2.9 and 2.5 gm. per cent in the albumin and globulin fractions respectively. Bone x-rays were normal. Sternal aspiration resulted in a specimen with very poorly represented granulopoiesis and erythropoiesis but with huge platelet masses and scattered intact megakaryocytes. (Fig. 4.) Sections of the spleen removed two years before were obtained. The spleen weighed 808 gm. and the microscopic examination showed active hemopoiesis. The changes were compatible with the diagnosis of agnogenic myeloid metaplasia without evidence of leukemia. The patient is essentially asymptomatic as far as her myeloid metaplasia is concerned but because of the extreme thrombocytosis she was treated with radioactive phosphorus. A slight decrease in platelets ensued although sufficient time has not elapsed to allow evaluation of the treatment.

Comment. This patient is one of three currently under observation who have had splenectomy. She has not demonstrated any adverse effects in the nearly three-year period since the removal of her spleen and, although she is a candidate for potential difficulties because of the thrombocytosis, her myeloid metaplasia must be considered asymptomatic. Thrombocytosis has been of common occurrence in our patients with myeloid metaplasia but the most striking increases in platelets have been noted in the three splenectomized patients.

DISCUSSION

The information obtained from a group of fifty-six patients with agnogenic myeloid metaplasia of the spleen permits the formulation of a composite clinical picture, subject to wide individual variations. A long history of symptoms referable to anemia or to pressure from a massively enlarged spleen is characteristic. Pallor, splenomegaly and, usually, hepatomegaly, but without significant enlargement of the peripheral nodes, are the principal physical findings.

Examination of the peripheral blood usually reveals a moderately severe normocytic, normochromic anemia with slight leukocytosis. Leukopenia is not infrequent and, while the total leukocyte count may be moderately elevated, levels commonly associated with chronic granulocytic leukemia are not ordinarily reached. Immature granulocytes, including myeloblasts and progranulocytes in small numbers, are, as a rule, present in the peripheral blood. Nucleated erythrocytes, in most instances, are found in small numbers although, as in Case v, they may be exceedingly numerous. A slight reticulocytosis



FIG. 4. The large platelet masses obtained by sternal marrow aspiration in Case VII; original magnification, $\times 300$.

is commonly seen even in the absence of evident hemolysis.

The erythrocytes demonstrate anisocytosis and bizarre variation in shape which is nearly always moderate to marked in degree. The changes in the red cells are often sufficient to suggest the diagnosis. It is tempting to attribute them to the extramedullary erythropoiesis. However, it seems more likely that the anisocytosis and poikilocytosis represent a manifestation of an abnormal proliferative process. The thrombocyte abnormalities are equally conspicuous. Platelets are frequently increased in number and occasionally to markedly elevated levels. Associated with the thrombocytosis is an abnormal morphology of the platelets, which also is probably best explained on the basis of a myeloproliferative disorder.

Examination of the bone marrow is essential in differentiating agnogenic myeloid metaplasia from chronic granulocytic leukemia. Marrow biopsy, as by a trephine needle instrument,³² often is more informative than aspiration alone. In agnogenic myeloid metaplasia the marrow is usually hypocellular and is frequently fibrotic but a specimen of normal or even increased cellularity is not incompatible with the diagnosis. Of more importance in differentiation is the absence of maturation defect or proliferation of an immature precursor of a single cell type.

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The frequent occurrence of large platelet masses in the marrow specimen deserves emphasis.

The demonstration of hemopoiesis in the spleen is required to establish with certainty the diagnosis of agnogenic myeloid metaplasia. In many instances, however, splenic aspiration or biopsy serves solely as confirmatory evidence and if such a procedure appears inadvisable for any reason a presumptive diagnosis may still be made on the basis of other findings. Continued observation in such cases is of the highest importance. Since confusion is most likely to arise between agnogenic myeloid metaplasia and early chronic granulocytic leukemia, the evolution of the latter illness will reveal the true diagnosis before the patient has been deprived of the benefit of specific antileukemic therapy. The potential dangers of the use of antileukemic agents in patients with agnogenic myeloid metaplasia should be recognized.

The treatment of myeloid metaplasia varies according to the major manifestations of the disease and must be individualized. In many instances only transfusions are indicated. Splenic radiation and splenectomy are not necessarily as noxious to the patient as was once thought.

In our series there are three patients who are surviving at eighteen, thirty-two and thirty-six months after splenectomy without either apparent beneficial or adverse effects, but with

greatly increased platelet counts. Aggravation of thrombocytosis with the possibility of thromboembolic complications has recently been emphasized.²² Splenectomy does appear to be an important therapeutic measure in certain selected patients with secondary hypersplenism usually manifested by hemolytic anemia and less frequently by thrombocytopenia. These patients should receive a trial of corticosteroid therapy and the decision to remove the spleen should be made only after careful consideration of all aspects of the individual case such as age, degree of splenomegaly, platelet status and the extent of myelofibrosis or osteosclerosis. It should be emphasized that the basic disease will not be beneficially influenced by this procedure. In place of splenectomy, splenic radiation may be of value in patients with massive splenomegaly and associated pressure symptoms. Radiation over the spleen has little if any appreciable effect on hypersplenic manifestations.

Hormone therapy is indicated chiefly for those patients with evidence of hemolysis and, as in Cases II and III, maintenance therapy with small doses of corticosteroids has been quite effective in controlling excessive red cell destruction with resultant symptomatic improvement and decreased need for transfusions. The corticosteroids otherwise have no apparent role in the treatment of myeloid metaplasia.

Radioactive phosphorus or total body radiation may be useful in suppressing platelet production in patients with marked thrombocytosis. Therapeutic agents such as vitamin B₁₂, folic acid, cobalt and iron are of no value.

Agnogenic myeloid metaplasia must be considered a progressive and eventually fatal disease, although the prognosis is better than that of chronic granulocytic leukemia. In the seventeen patients in our series in whom the total duration of symptoms and signs of illness is known, the course has varied from one to seventeen years, a figure which agrees closely with those reported by others.

It is appropriate to consider the question, "What is myeloid metaplasia?" It has been pointed out by Dameshek³¹ that bone marrow cells may proliferate as a unit or *en masse* rather than as single elements alone. This type of proliferation involving not only hemopoietic but stromal cells with the predominance of one or more cell types over the others would explain the multiple findings and the varied individual manifestations. Marrow fibrosis, therefore, would

be secondary to fibroblastic proliferation and the extramedullary hemopoiesis the result of the proliferation and resumption of the embryologic multipotentialities of the mesenchymal reticulum cells in the spleen and elsewhere. Is, then, agnogenic myeloid metaplasia an atypical form of leukemia possibly resulting from marrow injury? This question cannot be definitely answered but myeloid metaplasia would appear to belong to, or is at least closely related to, the general group of myeloproliferative disorders including polycythemia vera, chronic granulocytic leukemia, essential thrombocythemia and erythroleukemia. It is associated with a proliferation of fibroblasts and undifferentiated multipotential reticulum cells with abnormal erythropoiesis, granulopoiesis and thrombopoiesis occurring in extramedullary sites. The basic stimulus to this proliferative process remains unknown.

SUMMARY

1. The diagnosis of agnogenic myeloid metaplasia was made in fifty-six patients observed at the University of Michigan Hospital between January, 1942 and June, 1955. The incidence is about one-third that of chronic granulocytic leukemia, the condition with which it is most likely to be confused.

2. A long history of symptoms due to anemia or massive splenomegaly is usual. Splenomegaly is the most constant physical finding. Hepatic enlargement is frequent.

3. There is usually a moderately severe normocytic, normochromic anemia with a variable degree of leukocytosis, although leukopenia is not uncommon. The very high leukocyte counts commonly found in chronic granulocytic leukemia when anemia is present do not occur in agnogenic myeloid metaplasia.

4. Immature granulocytes and nucleated erythrocytes are, as a rule, present in the peripheral blood in small numbers. Moderate to extreme variation in the size and shape of the erythrocytes is nearly always evident and may be the means of suggesting the diagnosis. Thrombocytosis and abnormal platelet morphology are usually conspicuous.

5. Marrow examination, preferably by trephine needle biopsy, is an essential diagnostic procedure. Splenic aspiration or biopsy is helpful but usually not required for the diagnosis. The bone marrow is most often hypocellular

and frequently fibrotic. Predominant proliferation or maturation defect of an immature precursor of a single cell type, as seen in leukemia, is not observed. Active myelopoiesis is present in the spleen.

6. Agnogenic myeloid metaplasia is a progressive and eventually fatal disease, although the prognosis is distinctly better than that of chronic granulocytic leukemia. No treatment may be required early in its course.

7. In patients with anemia due to impaired erythrocyte production, transfusions are usually the only indicated therapy.

8. Judicious radiation over the spleen may be of value in patients with marked splenomegaly and associated pressure symptoms.

9. Corticosteroids are useful in controlling the hemolytic process which is prominent in some patients with agnogenic myeloid metaplasia but the need for continued administration may be anticipated.

10. In certain selected patients with dysplasia, manifested by hemolysis or thrombocytopenia, splenectomy may be helpful. Although splenic radiation or splenectomy is not necessarily deleterious to the patient, as was formerly thought, removal of the spleen aggravates the usually already existing thrombocytosis and thus may increase the hazard of thromboembolism.

11. Agnogenic myeloid metaplasia appears to be a specific entity possibly related to but distinct from leukemia. It is most likely a manifestation of a myeloproliferative process involving all elements, both hemic and stromal, which develop from the myeloid reticulum.

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Seminar on Bone Diseases

Emerging Concepts of the Structure and Metabolic Functions of Bone*

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WITH the advent of the atomic age there has occurred a revival of research interest in bone structure and metabolism. This interest stems in part from widespread concern over the potential radiation hazard of bone-seeking radioactive fission products—the “ashes” of atomic piles and bombs—and, in part, from low-cost radioisotopes suitable for the study of bone now made generally available by the chain-reacting pile. Whatever the reasons, the “bone field” has suddenly taken a new lease on life and is now bounding along at such a pace one has difficulty keeping abreast of the literature. Long-standing concepts have been swept away in the rush and only a few sound concepts have evolved to fill the resulting vacuum. Thus we are in possession of more data than knowledge, more facts than understanding [1].

In such a condition of flux it is difficult to construct a “story” of bone that makes sense and is, at the same time, accurate. An attempt to do just this will be made here, but the reader is cautioned that the story to be given is like current price lists—“subject to change without notice.” It is hoped that this story will serve as a temporary structure in which thoughts can be reoriented and plans for the future made.

THE CHEMISTRY AND ULTRASTRUCTURE OF BONE

Only recently have methods become sufficiently refined to permit a physical and chemical description of the crystals of bone mineral and to suggest the nature of their interrelations with the organic and water phases of bone.

The Bone Mineral. It is now generally accepted that the bone mineral is a single crystal-type [1a]. From all sources, bone crystals give an

x-ray diffraction pattern which is characteristic of a structure the mineralogists term the *apatite lattice*. This lattice, or space arrangement of ions, is common to a whole series of solid calcium phosphates whose molar ratio Ca/P varies from 1.3 to 2.0. Just how various preparations of calcium phosphate can all exhibit the same space arrangement of ions and yet vary in composition is a problem which engendered long and sometimes heated debate. It now appears that the lack of fixed stoichiometry can be attributed to the extremely small size of the crystals.

Low angle x-ray scatter, electron microscopy and measurements of specific surface area (M^2/g) are in substantial agreement; the microcrystals are of colloidal dimensions—only a few hundred Ångströms in length and breadth [2,3,4]. There is some disagreement as to the shape of these colloidal crystals but the most reasonable and best-supported proposals are those [3,5] which suggest that the crystals are tablets or plaques 200 to 300 Ångströms in length and breadth, with a thickness of only 20 to 50 Ångströms!

From crystallographic considerations, such tiny particles must exhibit unusual properties because of their size alone. All crystals exhibit an electrostatic asymmetry at their surfaces. Inside the crystal each cation is surrounded by a restraining field of anions and, conversely, each anion is surrounded by cations. At the surface, however, each ion is surrounded by oppositely charged ions *on one side only*. There results a residual charge or valency on the crystal surface. There are a number of means by which a crystal can lower its surface asymmetry or surface energy to attain greater stability: (1) lattice distortion, (2) lattice-defects (vacant ion posi-

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tions), (3) polarization of the surface ions, or (4) chemisorption of oppositely charged ions [6]. In large crystals these compensations are all possible and aberrant surface composition does not significantly affect the composition of the whole. Lattice distortion, lattice defects and, to

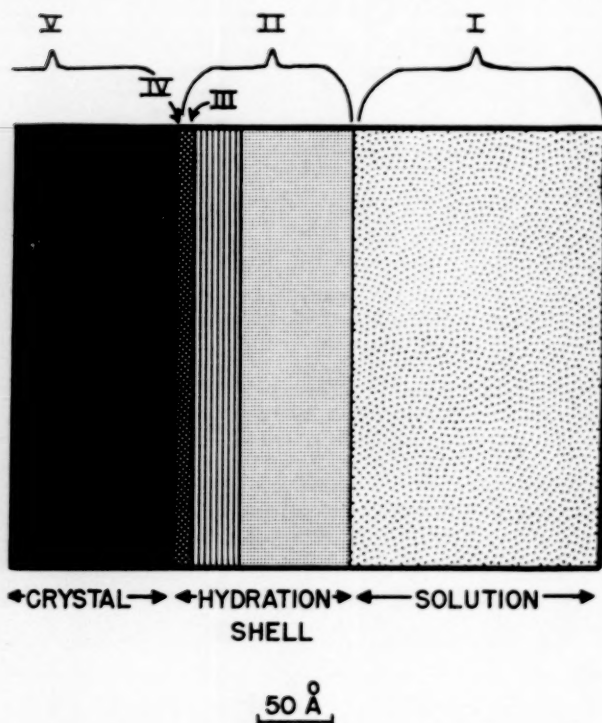


Fig. 1. A diagrammatic representation of the crystal solution interface. The various layers are illustrated and numbered according to usage in present discussion: I, the solution in bulk; II, the hydration shell comprised of three layers, loosely held water, tightly bound water, and the hydrated ion layer (III); the lattice surface, IV; and the crystal interior, V.

some extent, polarization of surface ions all require a "depth action," the crystal must have dimensions greater than 100 Å [6]. These alternatives are not possible in the tiny plaques of bone and as a result chemisorption is the principle means by which these crystals can stabilize. This results in a variable surface composition and since the crystals are largely surface (200 to 300 M²/g.) the overall composition is variable. These same surface forces bind to the surface a layer of hydrated ions and a shell of water which may exceed the dimensions of the crystal itself. For example, synthetic apatite crystals bind 0.8 gm. of water per gm. of crystals [7]. Because of the difference in density this represents a volume of water over two times that of the crystals!

Throughout the life of the crystal all its

reactions, growth, maturation and dissolution involve the transfer of ions across the crystal-solution interface, which is illustrated diagrammatically in Figure 1. Our knowledge of this ion-transfer has been extended by the use of radioactively-labelled ions [8]. Apparently any solute ion from the bulk solution (I) can penetrate by diffusion the outer layers (II) of the hydration shell [9]. At the crystal surface there is a bound layer of hydrated calcium, phosphate and hydroxyl ions (III) which are constantly interchanging with similar ions in the surface layers of the lattice (IV). Due to the presence of vacant lattice positions there is also a constant though much slower ion interchange within the crystal itself (V) [8,10]. Thermal vibrations permit an adjacent ion to pop into the "hole" causing the "hole" to migrate. These three processes are defined and used subsequently in the following terms: (1) diffusion into the hydration shell, $I \leftrightarrow II \leftrightarrow III$, (2) exchange between surface and the bound ion layer, $III \leftrightarrow IV$, (3) intracrystalline exchange or recrystallization, $IV \leftrightarrow V$. All three processes decline in rate and degree with increasing age and size of the crystal.

In the animal, the crystals are not exposed to pure water but rather to a solution of many different ions. Some of these can penetrate only the hydration shell, some can penetrate the surfacebound ion layer or the lattice surface by displacing either calcium, phosphate or hydroxyl ions, and some can penetrate into the crystalline interior. Such ion-exchange reactions, as summarized in Table I, account for the observed composition of bone mineral and its variability. Thus the carbonate content of bone is a reflection of the $\frac{CO_3^{--}}{HPO_4^{--}}$ ratio in serum as predicted from exchange theory [11] and as observed in rats on different dietary regimens [12].

Because the crystals vary in size and composition they must necessarily evince variable solubility. This has caused great confusion among researchers who would prefer to work with a more definitive system which follows solubility product principle. Recent work has shown, however, that the upper limit of stability of solutions containing calcium and phosphate ions is governed by the K_{sp} of $CaHPO_4 \cdot 2H_2O$, secondary calcium phosphate, which must be exceeded before spontaneous precipitation can occur [1a,13]. Since the thermodynamic ion product, $A_{Ca^{++}} \cdot A_{HPO_4^{--}}$, of normal serum is less than half the K_{sp} of $CaHPO_4 \cdot 2H_2O$, serum is

undersaturated [13]. It was also shown that when secondary calcium phosphate is precipitated at physiologic pH it is unstable and hydrolyzes spontaneously to hydroxy apatite. Further, though its solubility is variable, hydroxy apatite preparations and bone mineral have never given in the laboratory dissolution values of calcium and phosphate as high as those of normal serum [1a,14,15]. This seeming paradox is resolved only by reference to the presence or absence of solid phase. Serum is undersaturated in the absence of solid phase (in this case CaHPO_4) but supersaturated in the presence of solid phase (in this case hydroxy apatite).

The conclusion that serum is normally supersaturated (because in the animal (mammals at least) solid phase is *always* present) with respect to $[\text{Ca}^{++}]$ and $[\text{HPO}_4^{--}]$ has important physiologic implications. In the first place, some cellular mechanism must be postulated by which such a supersaturated condition can be maintained *in vivo*. Secondly, the driving force of the mineralization process is easily seen to be present in serum itself. Given a "seed" crystal, the serum will carry it spontaneously to full mineralization. Thirdly, some active cellular mechanism must be present in the intestine to permit the absorption of calcium against an ion-gradient.

The Organic Phase. Nearly all the protein present in bone is in the form of collagen, about 95 per cent of the fat-free organic content. Though the collagen of bone has received very little attention, great progress has been made in our knowledge of the structure of collagens derived from other sources [16]. Apparently, the cells secrete tiny proto fibrils or molecules which have the potentiality of self-aggregation [17]. There are several possible states of aggregation but under physiologic conditions only "normal" collagen structure is observed: Fibers about 800 Ångstrom units wide, of indefinite length with dense cross-banding seen at about 640 Ångstrom intervals along the length of the fibers [3]. The fibers are actually crystalline, giving a characteristic x-ray diffraction pattern [16]. Collagens from different sources all show the same crystallographic and morphologic appearance. They also are rich in aromatic amino acids, in glycine and pyrrolidine amino acids and are hydrolyzed by the specific enzyme collagenase [16]. However, there are differences in composition and reasons to believe that collagens from different sources may possess specific chemical properties. Once secreted, the collagen fiber undergoes no ap-

preciable "turnover" as do other body proteins [18]. Apparently the collagen is more or less dormant for the entire life of the bone osteone in which it resides.

The remainder of the organic portion of bone is poorly understood and "by definition, cannot

TABLE I
A SUMMARY OF ESTABLISHED ION-EXCHANGE
REACTIONS IN BONE MINERAL

Ion	Lattice Ion Displaced	Penetration into		
		Hydration Shell (ii)	Crystal Surface (iii + iv)	Crystal Interior (v)
K^+	—	+	—	—
Na^+	Ca^{++}	+	+	—
UO_2^{++}	Ca^{++}	+	+	—
Sr^{++}	Ca^{++}	+	+	+
Ra^{++}	Ca^{++}	+	+	+
Ca^{45++}	Ca^{++}	+	+	+
Cl^-	—	+	—	—
CO_3^{--}	PO_4^{--}	+	+	—
Citrate $^{--}$	PO_4^{--}	+	+	—
$\text{P}^{32}\text{O}_4^{--}$	PO_4^{--}	+	+	+
F^-	OH^-	+	+	+

be defined" [19]. We term it ground substance. It consists mostly of polymers of glucuronic acid and hexosamines. Both sulfated and unsulfated forms are present and make up a little less than 5 per cent of the dry fat-free weight of bone. It seems reasonable to assume that the degree of polymerization of the polysaccharide components directly affects the permeability and fluid interchange in bone. Not all the carbohydrate present should be considered as separate from the collagen fibers. Even on repeated purification, collagen fibers retain an irreducible minimum content of amino sugars. Of special interest is that reconstituted collagen fibers contain [13] traces of a phosphorylated amino sugar [20] of possible significance in the mineralization process.

Interrelations between Phases. Early workers described a preferred orientation of the crystallites with the long axis of the bone [27]. This now appears to be a reflection of a close association between the crystals and the fibers at the ultra-microscopic level. Electron microscopists, while differing in their opinion as to exact crystal morphology, all agree that the crystallographic c-axis closely parallels the longitudinal direction

of the collagen fibers [2,3,22]. Moreover, convincing electron micrographs [3] show that the tabular crystals lie in or on the collagen fibers between the major striations which occur at 640 Ångströms. In dentine, where the fibers have been cross-sectioned, isolated fields show the crystals *on edge* randomly arranged within the fiber bundles [5]. This dramatic finding has not been seen yet in bone. There is some evidence that, with increasing age of the osteone, both the crystals and the fibers continue to aggregate [23].

Such a close physical association between the fibers and the crystals has given great encouragement to those who believe that a *chemical* interaction occurs between the two phases.

The Water of Bone. In the past it was assumed that the water of bone was largely interstitial—extracellular fluid which helped to fill up the physical volume occupied by the bone. There are, indeed, spaces to be filled. With the discovery that apatite crystals bind large amounts of water, this view had to be revised. Unfortunately, the actual state of water in bone has not been clarified. The water content varies from 60 per cent in forming bone to 10 per cent in senile cortical bone. At no stage, however, is there sufficient water present to hydrate the crystals fully and it must be assumed that nearly all the water of bone is *bound water*. In support of this is the finding that little or no water can be removed from finely divided bone powder by enormous centrifugal fields, forces more than sufficient to remove interstitial water [7]. A traditional procedure for estimating the “interstitial” water of bone is to perform a chloride analysis and, on the assumption that the crystals do not contain chloride, the chloride space can be calculated. It is true that the crystals do not take up chloride but their hydration shells are freely permeable to chloride ion [9]. Therefore, a chloride analysis does not differentiate between interstitial water and bound water. Such calculations of interstitial water should now be considered meaningless.

In senile cortical bone it has been found [24] that the total water present can be accounted for as cellular and interstitial water attributable to the osteocytes and perivascular spaces. An examination of bones of different ages showed an inverse relationship between ash and water content as though, volume for volume, the growing crystals displace virtually all the water, leaving a solid, inert, unhydrated mass of crystals and fibers [24].

As has been seen, a number of recent advances have been made which depart sharply from older concepts. Normal serum has been proved to be supersaturated. The crystals have been proven to be variable in composition and therefore to evince aberrant solubilities (no K_{sp}). The interaction between collagen and bone crystal has been shown at the molecular level. These newly established facts have called for an “agonizing reappraisal” of established concepts of the normal physiology of the skeleton.

PHYSIOLOGIC ASPECTS

Since Aub's classic studies [25] and, later, those of Hevesy with radiophosphate, physiologists have realized that bone mineral is not dormant and inert but rather is constantly “turning over” and, throughout the lifetime of the animal, is participating in electrolyte metabolism. It has been a great struggle to deduce just what molecular events are involved in this ill-defined “turn-over process.” Even now, they are only dimly perceived.

Osteone Maturation and Reactivity. The three ionic processes already described: (1) diffusion into the hydration shell, (2) ion-exchange or ion-displacement at the crystal surface, and (3) thermal recrystallization within the crystal, all occur in the animal but they are modified under the influence of physiologic conditions. Superimposed on these passive, physicochemical events are such active processes as growth, resorption and translocation of bone. At the level of the osteone, age is the primary determinant of chemical reactivity. Newly deposited crystals are highly hydrated, extremely imperfect and nearly all of their ions are capable of rapid displacement [10,27]. As the osteone ages the crystals become larger, less hydrated and more perfect internally. The rates and extent of diffusion, exchange and recrystallization decline. In fact, it appears that the newly forming osteone very quickly mineralizes to nearly 90 per cent of its maximal mineral content [28]. Thereafter, further crystal growth is quite slow despite the great supersaturation of the circulating fluids. At 90 per cent of full mineralization there is very little free water, interstitial or bound, and the penetration of ions is slowed immensely. At full mineralization, physicochemical reactions grind to a virtual halt. Such old bone elements do not participate in the general metabolism and, in recent literature, have been referred to as “unavailable” bone [1a].

This, then, is the pattern of bone maturation: because of the supersaturation of the circulating fluids, the crystals continually grow, though ever more slowly, to the complete or near-complete exclusion of water. Here one might logically ask why, in the adult skeleton, *all* the osteons haven't become frozen and inert. The reason, of course, is the pattern of Haversian remodelling by which erosion cavities are continually forming and new Haversian systems developing [29]. This most important evolutionary development assures even the adult, non-growing animal a fresh supply of metabolically active bone. Further, despite the obvious fact that the proportion of the skeleton which is old, and therefore inert, increases steadily with advancing age* the increase in mineral content offsets this change and there results an almost constant supply of active exchangeable bone mineral throughout life [30].

It would therefore be expected that a radioisotope of any element which specifically enters into an ion-displacement reaction with bone crystals would show a characteristic pattern of histologic distribution in the animal. This distribution would reflect the patterns of growth and Haversian remodelling, the greatest concentrations of isotope coinciding with the most actively growing and most recently deposited bone elements. Such a characteristic pattern has now been observed with a large number of radioactive ions [1a] and it is of interest that the same histologic distribution (identical with that of Ca^{45}) is observed whether the isotope is administered to the animal or a section of bone removed from the animal and merely dipped in radioactive buffer *in vitro* [31,32].

Another group of radioelements which concentrate in bone are the transuranic elements and the rare earths. The pattern of histologic distribution of this group is also characteristic but quite different from that of Ca^{45} . The mechanisms underlying the skeletal deposition of these elements are unknown.

Mobilization of Skeletal Depots. We have discussed the pertinent facts governing the rapid

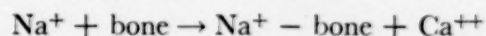
* The available skeleton is easily measured by means of radiosodium by a comparison of the specific activity of bone with the specific activity of serum. Since the isotope concentration quickly attains the same value in the available bone as in serum, the ratio $\text{SA}_{\text{bone}}/\text{SA}_{\text{serum}}$ gives directly the proportion of bone sodium (and therefore bone mineral) which is available. This ratio declines from 0.8 in infant rats to 0.3 in adult rats, dogs and humans [1,30].

interchange of ions between the bone crystals and the circulating fluids. The practical question arises as to the physiologic significance of these processes. The skeleton, in mass, represents a tremendous mineral and alkaline reserve; can these stores be called upon to meet the stress of electrolyte imbalance? We know from recent investigations that the available skeletal mineral can and does participate in buffering against shifts in the ionic composition of the extracellular fluid but the extent to which the skeleton can participate and the underlying mechanisms are poorly understood.

Some time ago transfusion experiments demonstrated that an amount of calcium three times that in the extracellular fluids was quickly mobilized from bone [33]. Conversely it has been shown in dogs that 27 mg. of an injected 90 mg. calcium is removed from the circulation by the skeleton in fifteen minutes [34]. Skeletal sodium, too, is quickly mobilized in response to acute, intraperitoneal dialysis [35]. The bone carbonate has been shown to be responsive to dietary changes [12] and even to changes in pCO_2 of the air breathed [36].

In theory, this buffering action of the skeleton should be passive and non-regulatory. Because the composition of the bone crystal is not fixed, it merely reflects, by ion-exchange, the composition of the fluid to which it has been exposed [1a]. For this reason the skeleton should *resist change only*. We should expect, therefore, when a patient suffering from prolonged dietary sodium depletion is placed on an adequate sodium intake that the skeleton will not help to restore normal sodium levels; rather, that the sodium-poor crystals should soak up large quantities of this ion and so delay recovery.

It is difficult to test theory in the animal. For example, the mechanism of sodium fixation involves an exchange for calcium:



In sodium depletion the reversal of this reaction would cause a withdrawal of calcium from circulation. Falling calcium levels would stimulate parathyroid hormone secretion. Since the mechanism of action of parathyroid hormone on bone is poorly understood, we find ourselves on a merry-go-round of ignorance. Subject, then, to secondary physiologic regulatory processes, bone-buffering can be considered analogous to a mineral bank where surpluses can be deposited and from which loans can be drawn.

This analogy is not strictly accurate, however, and requires the addition of a statute of limitation. At any given time, the available skeleton is comprised only of immature osteones which are forming or recently formed. Their composition reflects only the recent electrolyte history of

TABLE II
PRECIPITATION SEEDING OF CALCIUM PHOSPHATE
MIXTURES [13]

Compound Added	Amount (mg./cc.)	Final Concentration			Degree of Precipitation
		Liquid Phase		Solid Phase	
		P $M \times 10^{-4}$	Ca $M \times 10^{-4}$	Molar Ca/P	
None (control)	...	33.2	20.0
Apatite.....	3.0	20.6	1.49	1.47	7+
Apatite.....	3.0	21.0	1.04	1.75	8+
Gelatin.....	3.0	34.0	19.5
Fibrin.....	3.0	32.6	20.2
Collagen*.....	3.0	29.6	13.0	1.43	1+

Note: Solutions buffered at pH 7.4. Mixtures equilibrated ten days at 25°C., filtered through molecular filters, and ashed. Initial calcium and phosphorus concentration just below point of spontaneous precipitation.

* Reconstituted fibers [17] from tendon.

the animal economy. This imposes a strict time limit on the recall of a surplus or the return of a deficit. Such surpluses or deficits are carried on the books for a short time only; thereafter, the account is closed by virtue of its burial in the unavailable skeleton as the osteones mature.

These shifts in electrolytes to and from the skeleton involve no real structural changes. In severe mineral depletion, of course, trabecular bone will actually be resorbed [25].

This maturation of osteones poses a most difficult problem to the radiation biologist. The atomic age, with its attendant exposure of increasing proportions of the world's population to increasing levels of fission products, is a real and growing radiologic hazard. Many of these fission products are bone-seeking elements and it would be highly desirable to develop methods by which these radioelements could be washed out of the skeleton. Unfortunately, because of the continuing maturation process, only osteones formed in recent weeks are in contact with the circulating fluids. With passing time the bulk of the radioactivity resides in the unavailable skeleton, out of reach of any conceivable therapy short of massive demineralization [37].

On the Mechanism of Calcification. Historically, the mechanism of calcification has commanded more attention, perhaps, than it deserved. The intriguing Robison Phosphatase Theory captured the imagination of many investigators for many years. Unfortunately, it was based on a false premise: that calcification involved a precipitation by locally exceeding a K_{sp} . The Robison Theory has now been discarded but no one has yet found the proper role for phosphatase. The demonstration of the structural interrelations between collagen fibers and the crystals [3,5,23] and the demonstration that serum is supersaturated [13,15] has sharply focussed attention on ways in which the collagen fibers can induce the formation of crystal nuclei [38]. Three mechanisms have been suggested: (1) that the collagen fibers of bone specifically possess the chemical property of inducing the production of crystal nuclei perhaps through the presence in the molecule of a phosphorylated amino sugar [1a,13,20]; (2) that, in cartilage, the protein is rendered "active" by the enzymatic transfer of a pyrophosphate group from adenosine triphosphate (ATP) to the protein [39]; and (3) that the active nucleation center in cartilage involves a complex between collagen and the mucopolysaccharide, chondroitin sulfate [40].

Actually, these three suggestions presume the protein component to be a part of the mechanism and all three imply that the protein "template" binds calcium ions in a special spatial arrangement. The first deals with mineralization in forming bone, the last two with the mineralization of cartilage. Bone osteoid in the normal animal mineralizes as fast as it forms, but there is a latent period in cartilage. Perhaps these are two different processes. Perhaps the collagen of cartilage requires a "booster mechanism" while that of bone does not.

A clear differentiation between these three possibilities should soon appear in the literature. Certainly making bone crystals from serum or serum-like solutions with non-vital, isolated preparations is now a common laboratory procedure [13,40]. Even collagen preparations from non-calcifying tendon show some ability to induce crystal-formation. This is illustrated in Table II [13] where it is shown that apatite crystals and collagen fibers induced mineral formation from otherwise stable solutions while fibrin and degraded collagen (gelatin) were unsuccessful.

On the Action of Parathyroid Hormone. Once one recognizes that serum is supersaturated, some cellular mechanism must be postulated by which this supersaturated state can be maintained. The secretion of the parathyroid gland and vitamin D and its analogues immediately assume a new dimension of importance because these two substances are the only known agents which can increase or even maintain normal levels of calcium.

One thing is certain, the Albright-Reifenstein concept [47] of parathyroid action is now outmoded [1]. While it served long and well as a scheme for integrating the medical literature, it would seem to be basically incorrect. This idea postulates a primary phosphaturic effect on the kidney (never proved) and further postulates that the resultant fall in $\text{Ca} \times \text{P}$ product causes bone mineral to dissolve, thus implying a fixed K_{sp} (non-existent). With this explanation, effects observed in bone are secondary and passive.

The classic demonstration [42] of direct dissolution of bone by transplanted parathyroid tissue has now been confirmed [43]. This evidence would be enough but it is further clinched by the demonstration of the full hypercalcemic effect of parathyroid extract in *nephrectomized* animals [44]. The direct action of parathyroid on bone can no longer be questioned. The action of the parathyroids on kidney is still unclear. Phosphate levels do rise in hypoparathyroidism, they do fall after treatment with extract. Crude extracts do induce phosphaturia in animals. Yet, three laboratories have shown that the ratio of hypercalcemic activity to phosphaturic activity varies widely with different extracts [45-47]. This suggests that the hypercalcemic principle has no inherent phosphaturic activity of itself. In view of the finding that tissues other than the parathyroids will, when subjected to standard extractions procedures, give degradation products which produce phosphaturia [48], the whole issue of renal effects is unclear. The parathyroids may elaborate two active principles: hypercalcemic and phosphaturic; it may also be that the phosphaturic agent is artefactual, produced by the rigorous extraction procedure. Only a successful isolation and characterization of the active molecules will settle this question.

The mechanism of the parathyroid's hypercalcemic activity was never clear. If serum must be maintained in a supersaturated state, it must perforce act on cells in the region of the available crystals to produce an ion-gradient opposing the gradient in calcium ions. Only two reasonable

alternatives suggest themselves: (1) the bone cells might secrete a specific chelating substance which is oxidized once it reaches the general circulation, or (2) the bone cells might secrete acid, setting up a pH gradient. At the moment, current literature is best summarized as support-

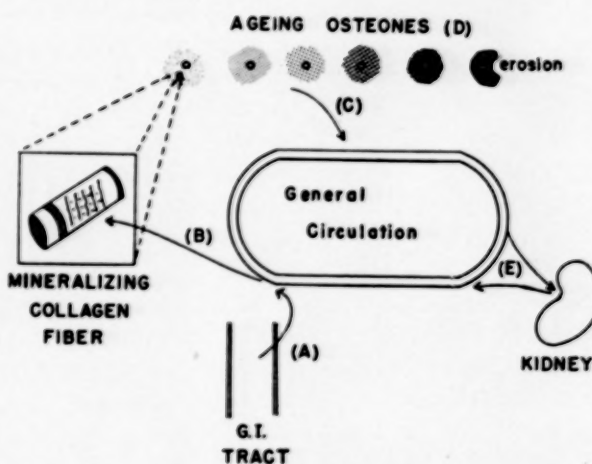


FIG. 2. A diagrammatic summary illustrating the four major postulates in present day views of bone metabolism.

ing a combination of these two alternatives [49]. Certainly there is mountainous evidence that citrate and calcium metabolism are closely interrelated [50]. Parathyroid secretion has been definitely shown to influence citrate metabolism [51]. Very recent preliminary results show a positive arteriovenous difference in citrate levels in the venous outflow from bone, a difference which increases promptly after the injection of parathyroid extract [49]. Citrate is certainly a good chelator of calcium [50], and it is rapidly oxidized by extracellular tissues. But, citrate could not be secreted by cells in any form other than the acid; otherwise, the cells would be rapidly depleted of intracellular cation. Thus it appears at present that parathyroid hormone acts by affecting the metabolic activity of cells.

SUMMARY

An attempt has been made to describe briefly the changing concepts of bone metabolism. Four new, important yet unproved postulates have been made and are summarized diagrammatically in Figure 2. The maintenance of normal bone physiology depends on:

1. The absorption of calcium and phosphate from the gastrointestinal tract. Since serum is supersaturated, some active mechanism or ion-pump must be postulated. Presumably, vitamin

D is required for the normal operation of this mechanism.

2. The mineralization of collagen. It is now fairly certain that the crystalline collagen initiates bone crystal formation. It is not yet settled whether the collagen molecule requires an "activation" mechanism.

3. The continuous transfer of ions to and from across the crystal-solution interface. Here, the crystals of the "available" bone reflect, by passive ion exchange, the electrolyte composition of the body fluids. It is necessary to postulate, however, that the osteocytes actively affect the composition of the fluid locally. Present indications are that local production of citric acid (possibly other acids) by the cells under the metabolic stimulus of parathyroid hormone (possibly also vitamin D) is responsible for maintenance of the serum in its supersaturated state.

4. The continuous formation, maturation and resorption of osteones. While the natural course of events is toward complete mineralization, a state of dehydrated inertness, new and maturing osteones continuously provide an "available" skeletal reserve of mineral which can passively buffer against changes in electrolyte balance.

5. The regulation of electrolyte composition by selective reabsorption in the kidney. This mechanism, with its intricate hormonal control is, of course, not a postulate [34,53].

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Clinico-pathologic Conference

Dyspnea, Weakness and Ocular Pain

STENOGRAPHIC reports, edited by Amoz I. Chernoff, M.D. and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient (No. 26906), a housewife fifty-two years of age, was admitted to Barnes Hospital on April 1, 1956. She died on May 3, 1956. Her chief complaint was weakness and shortness of breath of eight years' duration.

As a child, the patient noted frequent sore throats and severe "growing pains." No other details were remembered regarding these illnesses. In 1936 she underwent a "subtotal hysterectomy for a tumor of undescribed nature." She was then relatively well until eight years prior to admission when she noted the insidious development of exertional dyspnea, paroxysmal dyspnea and orthopnea with ankle swelling which was ascribed to "heart dropsy" and hypertension. Therapy with digitalis, sodium restriction and occasional injections of mercurial diuretics was moderately successful but the symptoms gradually progressed. Five years prior to admission, while testing her diabetic husband's urine, she tested her own and found a "trace of sugar" to be present. Diabetes mellitus was confirmed by her private physician and insulin but no diet was prescribed. She tested her urine each morning but took insulin only when glycosuria was noted. During the past few years it had been necessary to administer insulin almost daily. During the year prior to admission, she had noted gradually increasing fatigability, asthenia and malaise which caused her to be virtually bedridden. Throughout this same period she had noted easy bruisability without other signs of bleeding except "bleeding piles." Five weeks prior to admission mid-epigastric pain developed which radiated through to the back. Simultaneously, extreme nausea and occasional vomiting occurred. Her stools became tarry. At that time there was a marked increase in her dyspnea, orthopnea and edema, and in addition there was swelling of the abdomen. The fluid retention did not respond to the admin-

istration of mercurial diuretics. One episode of hemoptysis occurred. About four and one-half weeks prior to admission sudden pain, tenderness, swelling and redness of the right eye developed. This was followed by total blindness in this eye. She was told by her physician that she had "flu" and that "pus" had gotten into her eye from her bloodstream. Local therapy with ointments and soaks did not appreciably change the symptoms related to her eye. A right temporal and retro-orbital headache developed. Because of marked dyspnea, weakness and pain in her eye she was brought to the Barnes Emergency Room. The only medications taken regularly by the patient were digitalis and insulin.

The family history revealed that her father had died of diabetes and her mother had died of a stroke. One sister was living with "dropsy."

Physical examination revealed the temperature to be 38.1°C., pulse 130, respirations 32, and blood pressure 120/80. The patient was a critically ill, pale, cold, diaphoretic woman in marked respiratory distress. There was periorbital edema and proptosis of the right eye with chemosis and conjunctival hypertrophy. The right cornea was cloudy with questionable pus in the anterior chamber. The globe was hard and tender, and there was no vision from this eye. The left pupil reacted to light. Examination of the left fundus revealed the arteries to be narrow, the veins full with some A-V nicking. Small hemorrhages and a few exudates were scattered throughout the fundus. The disc was flat. Examination of the ears and nose was normal. The tonsils were large but were not inflamed. There was no enlargement of the lymph nodes. The skin was pale, dry and of poor turgor. Ecchymoses were noted over the buttocks but no petechiae were seen. The neck was supple and the trachea

was in the midline. There was marked venous distention of the neck veins while the patient was in the semi-erect position. The respiratory excursions were symmetric. Examination of the breasts revealed no abnormalities. Percussion and auscultation of the chest revealed the lungs to be clear. The left border of cardiac dullness and the point of maximum impulse were in the sixth left intercostal space, 14 cm. from the mid-sternal line. Sinus tachycardia was present. The heart sounds were of fair quality and a grade 3, rough, blowing, systolic apical murmur was heard which radiated to the left axilla. A similar murmur but of longer duration was heard in the aortic area. No diastolic murmurs were noted. No thrills were felt. The abdomen was distended with ascites. The liver was smooth, soft, slightly tender, and tremendously enlarged extending to 21 cm. below the right costal margin. No other organs or masses were felt. The rectal examination revealed large, tender, external hemorrhoids. No masses were felt. Pelvic examination was not performed. There was 2 plus soft pitting edema extending from the feet to the lower abdominal wall. The peripheral pulses were palpable. There was marked pallor of the nail beds but no clubbing. Except for mild obtundity and changes associated with the right panophthalmitis, the neurologic examination was not remarkable.

Laboratory data were as follows. Hemoglobin, 6.4 gm. per cent; red blood cell count, 2 million per cu. mm.; packed cell volume, 22 per cent; white blood cell count, 9,800 per cu. mm.; platelets "adequate"; reticulocytes, 8.7 per cent; differential: 66 per cent segmented forms, 2 per cent band forms, 23 per cent lymphocytes and 9 per cent monocytes. The erythrocytes revealed polychromasia and moderate anisocytosis. The mean corpuscular volume was 110 μ ; mean corpuscular hemoglobin, 33 gamma gamma; mean corpuscular hemoglobin concentration, 29 per cent. Urinalysis: specific gravity, 1.017, reaction acid, 2+ protein, negative sugar, negative acetone; on microscopic examination there were occasional hyalin and granular casts, many white blood cells with occasional clumps, and an occasional red cell. The urine was negative for bile; the test for urobilinogen was 1 plus in a 1:2 dilution of urine and negative in a 1:4 dilution. No 5-hydroxy indole acetic acid was present in the urine. Stool: tarry in consistency and color and the guaiac reaction was strongly positive. The cardiolipin test was negative. Non-protein ni-

trogen, 56 mg. per cent; fasting blood sugar, 184 mg. per cent; sodium, 128.6 mEq./L.; potassium, 5.4 mEq./L.; chloride, 84 mEq./L.; CO_2 21.2 mEq./L. Total protein, 5.4 gm. per cent, albumin 3.0 gm. per cent, globulin, 2.4 gm. per cent, alkaline phosphatase 2.5 Bodansky units. Cephalin cholesterol flocculation test 3+; thymol turbidity 0.9 units; total serum bilirubin less than 0.8 mg. per cent; prothrombin activity 22 per cent. Bromsulphalein, 4.5 per cent retention in forty-five minutes. Electrocardiogram: ST segment and T wave changes were compatible with digitalis effect, full AV conduction, and sinus tachycardia. Chest film: cardiac enlargement, left and right sided; infiltration, left upper lobe (probably pneumonitis); pulmonary vascular congestion, bilateral. Venous pressure: 290 mm. of saline. Decholin® circulation time: fourteen seconds. Urine culture and two blood cultures revealed no growth.

The patient was maintained on therapy consisting of digitoxin, 0.1 mg. daily, sodium restriction, and a diabetic diet with carbohydrate restricted to 140 gm. daily. After cultures were obtained, she was given penicillin, 400,000 units, and streptomycin, 0.5 gm., intramuscularly every six hours. Although the patient received five units of packed cells (through venous pressure sets) during the first five days of hospitalization, the hemoglobin increased only to 8.1 gm. per cent. The feces remained positive for occult blood. However, the infrequent bowel movements made it difficult to determine the activity of the bleeding by this method. Following two more units of packed cells, the hemoglobin rose to 9.5 gm. per cent and thereafter slowly increased to vary between 11 and 13 gm. per cent during the remainder of the hospitalization. The venous pressure remained about 250 mm. of saline, but the circulation time rose to thirty-six seconds. The dyspnea was markedly improved during the first few days of hospitalization, but was intermittently present throughout the patient's course.

On the tenth hospital day, an upper gastrointestinal series revealed extrinsic pressure on the fundus of the stomach and on the distal esophagus thought to be due to cardiac enlargement. There was edema of the intestinal mucosa, calcification of the abdominal arteries and ascites. On the sixteenth hospital day a barium enema was interpreted as showing carcinoma of the rectosigmoid. On the eighteenth hospital day

an abdominal paracentesis was done. Only 100 cc. of straw-colored peritoneal fluid was obtained. Studies on this fluid revealed a specific gravity of 1.022, protein 2.2 gm. per cent, 1,877 red cells per cu. mm. and 34 white cells per cu. mm. Cultures were negative. There was an inadequate amount of fluid for cytologic examination.

During her hospitalization the major problem was severe dyspnea, although auscultation of the chest never revealed more than a few rales and a few coarse rhonchi. The patient was cyanotic except when receiving oxygen by tent or nasal catheter. Cautious attempts at increasing the dosage of digitalis were unsuccessful in reducing the venous pressure or preventing attacks of dyspnea. Mercurial diuretics alone or with ammonium chloride and aminophyllin never produced a significant diuresis. The patient's weight decreased 11 pounds during the first three weeks of hospitalization, but the edema persisted. The fluid intake varied from 1 to 2.5 L. per day; the urine output averaged about 1 L. per day. The patient perspired profusely even when afebrile. The non-protein nitrogen fell initially to 27 mg. per cent and rose to 71 mg. per cent during the last week of her life. The temperature varied from 37° to 39°C. during the first week, was seldom greater than 38°C. during the second week, after which time she was afebrile. The dosage of penicillin and streptomycin was decreased by half after the first week, and penicillin alone was given following the second week. The inflammatory changes in the right eye subsided somewhat, but there was no return of vision. Repeated sputum studies for acid fast organisms were negative. On the twenty-sixth hospital day, a sputum culture revealed an almost pure growth of a coagulase negative staphylococcus aureus. Erythromycin, 0.25 gm. every six hours, was added to the penicillin coverage. On the thirty-first hospital day she seemed to be somewhat improved. There was considerably less respiratory distress and she no longer required oxygen therapy. The temperature spiked to 38.8°C., but there was no change in physical findings. The white count was 10,700 per cu. mm., the hemoglobin 11.8 gm. per cent. On the thirty-second hospital day the temperature suddenly rose to 39.6°C., the blood pressure fell to shock levels, and the patient died. Aside from the return of severe dyspnea there were no other symptoms and no preterminal changes in the physical findings.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: This case will be discussed under the following headings: first, the cardiac lesion; next, the nature of the pulmonary disease; third, the eye lesion and lastly, the nature of the gastrointestinal disease and the cause of the bleeding. Let us consider the nature of the cardiac lesion. Dr. Kingsland, the history relates that the patient had frequent sore throats and severe growing pains as a child. We have no details about the growing pains except that they were severe. "Growing pains" in a child are commonly believed to represent a manifestation of the rheumatic state and I wonder if you would comment upon the significance of this finding.

DR. ROBERT KINGSLAND: One would be hesitant to make the diagnosis of rheumatic fever on this basis alone. Of course in a woman in whom congestive failure later develops it certainly has much more importance.

DR. REINHARD: I was very much interested in the relationship between growing pains and the rheumatic state. I wondered what the pediatricians thought about this concept so I consulted Dr. Goldring and Dr. Klingberg of our Pediatrics Department and they both believe the character of the pain is crucial. The average child who is stated to have growing pains really has muscle pains. These tend to come on in the late evening or even at night. Very often the pain has the characteristics of a "charleyhorse" and is relieved by massage. These pains have nothing whatsoever to do with the rheumatic state. On the other hand, true rheumatic pains are more localized in the joint and do not necessarily come on in the late evening or at night. They are not muscular pains and are not relieved by massage. In the absence of any detailed history about the character of the pains experienced by this patient all one can say is that the majority of so-called growing pains are not truly rheumatic and that the significance of this point in the history must be questioned. If we accept the concept that the growing pains were not of rheumatic origin we are left without any history suggestive of acute rheumatic fever.

Symptoms of congestive heart failure first developed eight years prior to the death of the patient at which time she was forty-four years old. The usual therapy for congestive heart failure was at first moderately successful but there was a gradual progression of the symptoms of

congestive failure in spite of digitalis, salt restriction and diuretics. When first seen by a physician for her cardiac symptoms eight years prior to her death, the patient was told that her blood pressure was elevated. Unfortunately we have no information about what happened to her blood pressure during the ensuing eight years nor do we know what the actual blood pressure reading was when she was first given this information. During the first week of her stay in the hospital her blood pressure was normal and thereafter it fluctuated between normotensive and mildly hypertensive levels. She was, however, severely decompensated throughout this period. At times the blood pressure rose as high as 170/100. This patient had a markedly enlarged heart, a loud grade 3 rough blowing systolic murmur at the apex and also a loud systolic murmur in the aortic area. One observer described a gallop. Several other observers stated that there was a sound suggestive of a gallop but that it was not a true gallop. No diastolic murmur was described. Dr. Smith, do you see any reason to doubt rheumatic fever as the etiology of the cardiac lesion?

DR. JOHN SMITH: No. One may fall back on this diagnosis even in the absence of a tangible history of rheumatic fever. The growing pains that she had in childhood may indeed have been muscle pains, not related to rheumatic fever. The appearance of the murmurs and the course of the disease suggests something of the character of valvular or endocardial disease coming on years later.

DR. REINHARD: Dr. Moore, you examined this patient and thought she had rheumatic mitral disease. Do you still support this diagnosis?

DR. CARL MOORE: Yes. One is also tempted to consider that she may have had more severe hypertension in the past and that there was a significant element of hypertensive cardiovascular disease. It is very difficult, when one reads the protocol, to make a firm diagnosis of rheumatic carditis, but if I remember correctly, everyone who saw this woman thought that in all probability she had rheumatic heart disease although in addition she may well have had some element of hypertensive heart disease.

DR. REINHARD: The chest films, which will be discussed in more detail by the roentgenologist, showed a very obvious and marked generalized cardiac enlargement. Dr. Massie, is there anything in the patient's electrocardiograms or in

the chest films which would help us arrive at an etiologic diagnosis of the type of heart disease?

DR. EDWARD MASSIE: No. The heart was grossly enlarged particularly in the region of the left ventricle. There was also evidence of pulmonary congestion but that is all that can be gathered from the roentgenograms. The electrocardiograms were abnormal but did not show evidence of coronary disease or anything specific except the effects of digitalis. If this patient did have hypertension we certainly do not have an explanation for the lack of hypertension at the time of her hospitalization.

DR. REINHARD: You do not believe that heart failure is sufficient to account for this observation?

DR. MASSIE: No. In congestive failure the blood pressure is just as likely to be maintained at the same or even higher level than before failure as it is of being reduced somewhat. However, the pressure would never be reduced to this level by failure alone. The evidence favors rheumatic heart disease.

DR. REINHARD: From previous clinico-pathologic conferences we know that in a patient who has clinical findings suggestive of rheumatic heart disease and who gives no history of definite rheumatic fever, postmortem examination may show findings which the pathologists are unwilling to call rheumatic valvular disease. These cases may come under the category of endocardial fibroelastosis. Dr. Sherry have you considered this diagnosis?

DR. SOL SHERRY: Yes.

DR. REINHARD: Would you like to comment?

DR. SHERRY: I believe it would be highly unusual for an individual with fibroelastosis to be in congestive heart failure for eight years. In most patients, once they go into the failure, the disease usually progresses quite rapidly even though there may have been evidence of cardiac enlargement for a number of years. On that basis I believe it would be highly unlikely for this patient to have had fibroelastosis.

DR. REINHARD: Dr. Wilbur Thomas studied a group of twenty patients with endocardial fibroelastosis and made some observations which I believe might be worthwhile reviewing at this time. He pointed out that although murmurs are by no means uniform in these patients, murmurs do occur. In nine out of the twenty patients there were cardiac murmurs. These were described as faint or soft systolic murmurs,

mostly at the apex in seven patients; there were loud systolic murmurs at the apex in two patients; and there was a short diastolic rumble in addition to a faint systolic murmur in one patient. It is also of interest that in eight of these twenty patients a gallop rhythm was detected. There was mild hypertension in two patients, a normal blood pressure in eight of the patients, and hypotension in eight others. The blood pressure was not available in two patients. One may therefore observe murmurs similar to those that were heard in this patient. One can see almost any kind of blood pressure. One may also hear a gallop in fibroelastosis. I would agree with Dr. Sherry that the one point that is against this diagnosis is the long duration of the cardiac failure but I do not have enough data to know just how rare it is for patients with this disease to survive for many years after cardiac failure first develops.

Let us go on to a consideration of the pulmonary lesion. You will recall that in addition to the symptoms that were presumably predominantly cardiac in origin, including the severe exertional dyspnea and orthopnea, the patient had one episode of hemoptysis occurring approximately five weeks prior to admission. This would appear to have been a true hemoptysis and not vomiting of blood. Dr. Benz, would you now discuss the chest roentgenograms?

DR. RICHARD BENZ: The first film of the chest was taken on April 6, 1956, and revealed marked enlargement of the cardiac silhouette, calcification in the aortic arch and a striate infiltration ending in a patchy infiltration in the left upper lung field. This infiltration appeared to abut on the pleural surface and had a somewhat triangular appearance. There was also, possibly, an infiltration in the right base as well as some pleural effusion on the left. The etiology is obscure. The infiltration was called a pneumonitis and could be on the basis of a pulmonary infarct. Other films taken on the same date, were in the supine position and showed that the left costophrenic angle was clear, which indicated that the fluid had reached a more dependent part. In the lateral projection one could identify the infiltration as being in the apical segment of the left upper lobe. Three weeks later portable films were taken which showed that the left upper lobe infiltration had not changed appreciably. The infiltration in the right lower lobe was more apparent. In the second set of films the infiltration was again called a pneumonitis with

the possibility of a metastatic lesion being considered.

DR. REINHARD: Before these last roentgenograms of the chest were taken, a gastrointestinal series had been obtained and these were interpreted by at least one of the radiologists as possible carcinoma of the rectosigmoid. The last chest film was interpreted by the same individual as representing possibly a metastatic lesion to the lung. Dr. Smith, would you tell us what you believe her pulmonary lesion to be.

DR. SMITH: The comments I made before were directed toward the early course of the patient. The picture had changed. There was calcium in the aorta and we know that diabetes was discovered, so that the possibility of coronary disease must now be considered. The pulmonary lesion is extremely interesting. It seems to me that the degree of dyspnea from which this patient suffered was out of all proportion to the abnormality of cardiac function. This observation brings up the problem of the dyspnea of pulmonary vascular obstruction. It is the sort of dyspnea occurring in individuals whose lungs have been showered with embolic particles or develop minute infarcts. The picture also reminds one of extensive and extreme pulmonary fibrosis. The question arises as to whether or not there is an acutely raised pulmonary arterial pressure which may stimulate the receptors to provoke this remarkable dyspnea. Since the possibility of carcinoma has been entertained, I wonder whether there has been a seeding of the lungs by metastatic lesions, or whether there has been an extensive thrombosis within the vasculature of the lungs which occasionally occurs in carcinomatous disease.

DR. REINHARD: The lesion in the left upper lobe of the lungs seen in the chest film has a triangular appearance which extends out to the pleural surface and looks like a characteristic infarct. In addition, you suggest that the symptoms would be entirely compatible with either multiple thrombi or emboli elsewhere in the lungs. What is the relative frequency of embolic phenomena in hypertensive, arteriosclerotic and rheumatic heart disease as well as in fibroelastosis. Is embolization merely a function of the duration of the congestive failure?

DR. SMITH: Pulmonary embolization is frequently related to congestive failure. The emboli arise peripherally under the influence of chronic passive congestion. It also occurs in auricular fibrillation which is likely to be found in any one

of these types of heart disease. Multiple emboli may also be part of any debilitating illness.

DR. REINHARD: In Dr. Thomas' article on fibroelastosis it was stated that in nine of twelve adult patients, mural thrombi were found in one or more chambers of the heart and eight of them gave evidence of embolization to one or more organs. These data give an incidence of emboli in approximately two-thirds of the cases. Admittedly this series is a small one but it suggests an extremely high incidence of embolic phenomena in association with this particular type of endocardial disease.

Dr. Harford, on the twenty-sixth hospital day the sputum culture yielded an almost pure growth of coagulase-negative staphylococcus aureus. What is the significance of this finding?

DR. CARL HARFORD: During the stay in the hospital the patient had an irregular low grade fever ranging between 37° and 38.5°C. with a terminal spike to 39.5°C. This patient had two sputum cultures. The first one was on the eighteenth hospital day in which a few coagulase negative organisms were found. In the second, on the twenty-sixth hospital day, profuse growth occurred but the coagulase test was not performed on this particular specimen. No sensitivity tests were performed. These findings are not decisive as to whether the patient may have had micrococcal pneumonia or not. It is perfectly possible that these organisms were what remained after the penicillin and streptomycin sensitive organisms were removed from the sputum by chemotherapy. These bacteriologic findings could be encountered in any patient with sputum on such chemotherapy even without a pulmonary lesion. On the other hand, we should not interpret the coagulase test in a rigid manner. There is a general correlation between the pathogenic micrococci and the coagulase test. However, in the lung, host factors of resistance are of such importance that we should not rule out the possibility that this organism may produce a pneumonia even though it is coagulase negative. In a patient who has diabetes, and who is in cardiac failure, the resistance is undoubtedly lowered.

DR. REINHARD: How often does one observe superimposed infection in an area of pulmonary infarction?

DR. HARFORD: All I can say is that it is frequent.

DR. REINHARD: Next, let us consider what happened in this patient's eye. She had pains,

swelling and blindness, which came on very suddenly. This sequence suggests that the eye lesion might also have been an embolic manifestation. Dr. Becker, would you discuss the patient's panophthalmitis?

DR. BERNARD BECKER: There is evidence from the history and from the physical findings that this patient had diabetic retinopathy. It is only fair to say that in a patient with diabetic retinopathy the commonest cause of an acute episode of pain and loss of vision in an eye would be hemorrhagic glaucoma. That is, glaucoma secondary to hemorrhage in the eye with newly formed vessels on the surface of the iris. The question in this particular case however is answered by the physical findings. The description of the amount of chemosis and of the nature of the ocular lesion is most suggestive of a panophthalmitis, and panophthalmitis is believed to be secondary to a bacteremia with localization of some pus forming organism within the eye. The only other possibility is the very rare episode of a metastatic lesion to the anterior segment of the eye, which can exactly simulate this situation.

DR. REINHARD: If this was an infectious panophthalmitis, why would the pain, swelling and blindness come on so rapidly? She apparently lost her vision almost completely in a very short period of time.

DR. BECKER: The eye forms an excellent culture medium and bacteria grow exceedingly well in the vitreous and aqueous humors of the eye.

DR. REINHARD: We now come to a consideration of the gastrointestinal lesion. Five weeks prior to admission to the hospital mid-epigastric pains developed which radiated through to the back. The patient also had nausea and vomiting which persisted. She had a severe hypochromic anemia at the time of admission to the hospital. She had a reticulocytosis of 8.7 per cent. Her stools were tarry and guaiac positive. I will therefore assume without further discussion that she had a bleeding gastrointestinal lesion. Dr. Benz, would you now discuss the gastrointestinal films?

DR. BENZ: The patient had to be examined in the semi-prone and semi-supine positions because of extreme dyspnea. In the upper gastrointestinal series there was a suspicious curvilinear density posterior to the stomach which displaced the esophagus somewhat to the right side. There may also have been some displacement of the small intestinal loops. On April 16, six days

later, the examination of the colon was performed and the lateral view of the rectum showed an area of constriction in the rectum. There is the possibility that the defect was due to an extrinsic lesion indenting this area. However, it appeared very typical of a carcinoma of the rectum. In trying to tie together the mid-epigastric pain, the suspected lesion in the mid-postgastric region, the chest film and the rectal lesion we suggest the possibility of a pancreatic tumor with implants in the rectosigmoid region and with metastases to the lung.

DR. REINHARD: Dr. Daughaday, are patients who have diabetes predisposed to carcinoma of the pancreas?

DR. WILLIAM DAUGHADAY: In the experience of the Joslin group carcinoma of the pancreas has been found in an inordinate number of their diabetic patients who have had an autopsy examination. It is certainly the belief that carcinoma of the pancreas is more common in diabetes. One might suspect that the relationship should be the other way around, that the patients initially had carcinoma of the pancreas which destroyed the pancreatic islet cell function. However, the histories of these patients were analyzed from this point of view and it was found that in most cases they had diabetes for more than two and one half years which is beyond the usual life expectancy of carcinoma of the pancreas. I believe, therefore, that the feeling now is that carcinoma of the pancreas is more common in diabetes. Any functional interpretation of why this should be is completely unknown.

DR. REINHARD: Dr. Duden, would you discuss this patient's symptoms in relation to the suggestion that has been made by the radiologist that she might have had a carcinoma of the pancreas. Is the type of pain suggestive of carcinoma of the pancreas?

DR. CHARLES DUDEN: Yes, it is very common for pancreatic disease, especially malignant disease or cystic disease, to produce radiation of pain straight through to the back.

DR. REINHARD: What do you believe is the cause of this patient's gastrointestinal bleeding?

DR. DUDEN: I would probably accept the diagnosis of cancer of the rectum. One cannot ignore the roentgenologic evidence, but there is some suggestion of extrinsic pressure on the rectum which might be seen with a lesion higher up. The palpation of the abdomen, the size of the liver, the venous thrombosis, all would be consistent with malignancy in the lower intestinal

tract, except for the fact that the stools were always tarry. It is difficult to accept bleeding of that type as coming from a rectal lesion. It directs one to a lesion higher up which was producing the bleeding.

DR. REINHARD: Dr. Eckert, do you have anything to add?

DR. CHARLES ECKERT: The surgical resident saw this patient in consultation and on rectal examination could not feel any intrinsic tumor nor could he feel a rectal shelf in the cul-de-sac. I believe it is hardly likely that she had an intrinsic tumor of the rectum. It would be most unusual to overlook such a lesion. On the other hand, extrinsic masses can easily be missed, particularly in an uncooperative patient. We cannot exclude the possibility of peritoneal metastases producing the defect which is seen on the roentgenogram. I am rather impressed with the evidence of a retrogastric mass. A tumor penetrating either the stomach or duodenum which is bleeding and producing a secondary anemia as well as the remaining symptoms would seem to be more likely than a lesion of the colon. Lesions within the colon that produce tarry stools and anemia are more common in the right side of the colon than in the left. They may be completely asymptomatic and still be responsible for an extreme anemia or for the presence of a large mass, hitherto unsuspected but found on routine physical examination. But we have no evidence that there is a tumor of the right colon and pretty good evidence against it. If one is looking for an occult cancer of the alimentary canal, cancer of the stomach is the primary tumor to consider. Second in importance is cancer of the pancreas. But cancer of the stomach outranks all others. Although adequate roentgenograms may have been taken, and adequate gastroscopy may have been performed, there are many cases that later prove to be cancer of the stomach in spite of the lack of positive findings. On the other hand, the factors in this case suggest that a lesion in the pancreas may be present.

DR. REINHARD: Dr. Eckert, I am profoundly disturbed that nothing abnormal was felt on the rectal examination. What was the cause of the amazing roentgenographic abnormality in the rectum or colon if it was not a primary tumor.

DR. ECKERT: One is much more likely to miss an extrinsic mass due to peritoneal metastases than an intrinsic lesion of the rectum.

DR. REINHARD: You believe that the degree of distortion was not great enough for it to be felt?

DR. ECKERT: I would have expected the abnormality to be felt but, once again, it can be missed. It is unlikely that a primary rectal cancer would be missed.

DR. REINHARD: Are there any further comments?

DR. BRUCE KENAMORE: I would like to suggest another possibility that would explain almost everything, that is, a dissecting aneurysm.

DR. REINHARD: Dr. Moore, I reviewed the roentgenograms and the peculiar curvilinear shadow in the upper abdomen is certainly not in the location of the abdominal aorta. It is high up in the abdomen but it does suggest a vascular arterial lesion. Dr. Wilson suggested that it might possibly represent an aneurysm of the splenic artery. Does this idea appeal to you?

DR. MOORE: It appeals to me much less than does carcinoma of the pancreas because I believe there are many things that one could explain on the basis of carcinoma of the pancreas such as the greatly enlarged liver. I do not see how one could account for the big liver on the basis of a dissecting aneurysm or any other kind of aneurysm.

DR. MASSIE: We would be very remiss not to mention subacute bacterial endocarditis. It is likely that the patient had rheumatic heart disease, mitral insufficiency, perhaps aortic stenosis and unexplained fever. She was told by her private physician that she had influenza and that pus had gotten to her eye from the blood stream. Perhaps it was actually the other way around. However, subacute bacterial endocarditis would not explain the gastrointestinal manifestations but the patient might have two independent diseases.

DR. REINHARD: How often does this type of panophthalmitis occur in subacute bacterial endocarditis?

DR. BECKER: I have seen septic emboli in bacterial endocarditis but I have never seen panophthalmitis in this disease.

DR. HARFORD: In view of all the talk about carcinoma, I would like to ask Dr. Becker if it is conceivable that the ocular lesion was actually the result of a cavernous sinus thrombosis.

DR. BECKER: No. I believe not if the patient has signs of pus within the eye. Cavernous sinus thrombosis might produce proptosis and chemosis but not a purulent endophthalmitis as described.

DR. REINHARD: I would like to suggest that this patient had severe chronic congestive heart

failure which on the basis of statistical probability was most likely due to rheumatic valvular disease. I am attracted by the possibility of endocardial fibroelastosis. I believe that death was due to multiple emboli coming from the heart leading to infarction of the lungs and perhaps of other organs as well. The gastrointestinal bleeding was most likely due to a carcinoma of the pancreas with seeding of the serosa on the rectosigmoid. The patient had a panophthalmitis. She had mild diabetes. I believe she had mild hypertension in the past not contributory towards her death. The patient had a urinary tract infection, possibly pyelonephritis, and terminal azotemia. She may conceivably have had a renal infarction.

PATHOLOGIC DISCUSSION

DR. F. KRAUS: At autopsy, the body was that of a well developed, moderately obese woman, with edema (two plus) of the ankles. The right eye was hemorrhagic and the scleras bright red but permission for the examination of head and eyes had been refused in this case. Five hundred cc. of serofibrinous fluid were present in the abdominal cavity and 100 cc. in each of the pleural cavities. The heart was enlarged, weighing 610 gm. Both ventricles were hypertrophied, the wall of the right measuring 6 mm. and that of the left 23 mm., but the right and left atria were of normal size. The aortic, tricuspid and pulmonic valves were not remarkable. The endocardium and all valves but the mitral appeared normal. The free edge of the latter valve was thickened and scarred. The chordae tendinae were thickened, shortened and in many places fused together. This lesion may be considered characteristic of chronic rheumatic endocarditis. In the center of the valve was present a large friable vegetation with fibrotic and hyaline borders with calcification in the deeper parts. Perforation of the valve had developed in the center of this lesion. (Fig. 1.)

The lungs were heavy (1,150 gm.), indurated and brown, indicative of severe chronic passive congestion. Firm rubbery nodules, granular on their cut surface, were scattered throughout all parts of the lungs, particularly throughout the upper lobe of the left side, suggesting bronchopneumonia. Pulmonary infarcts were not detected grossly.

Edema and congestion were present throughout the entire gastrointestinal tract, with petechiae in the walls of the stomach and entire

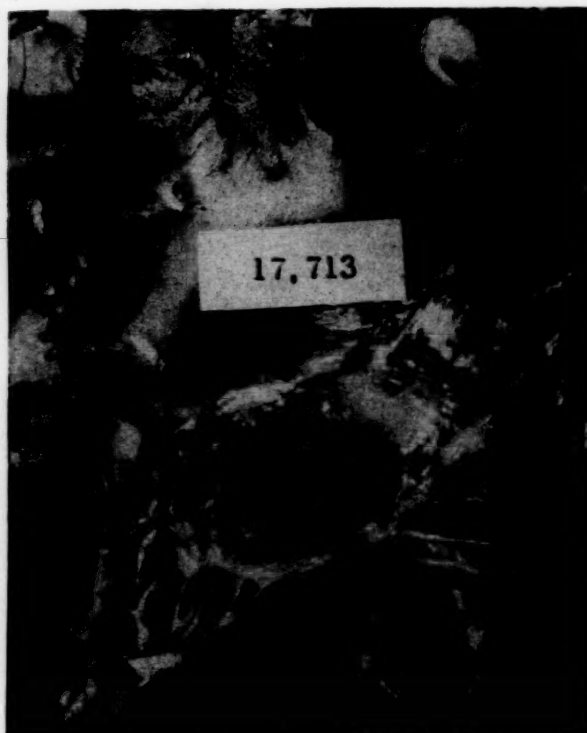


FIG. 1. The anterior leaflet of the mitral valve bears a friable vegetation, with necrosis and perforation in the central part of the lesion. The chordae tendineae are thickened, fused and shortened.

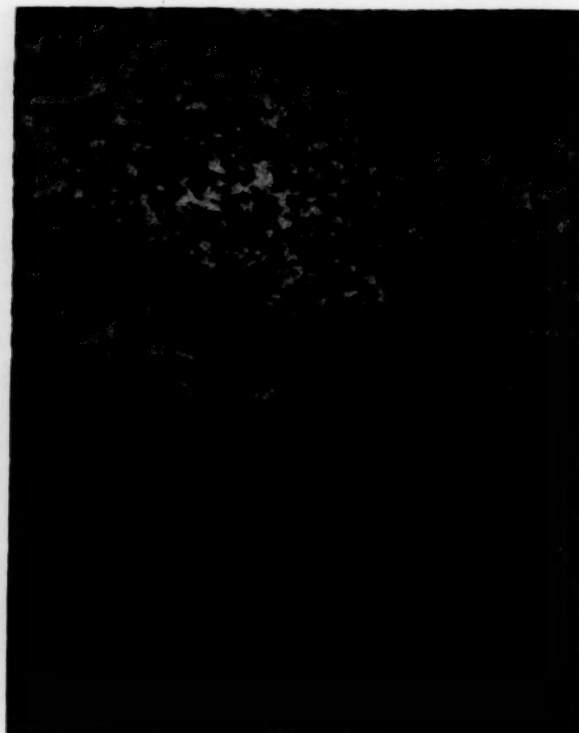


FIG. 2. There is necrosis of the valve substance at the bottom of the photograph, with a polymorphonuclear leukocytic infiltrate around this area and superficial deposition of fibrin. Bacterial colonies were demonstrated within the area of necrosis and in the fibrin. Hematoxylin and eosin stain, $\times 100$.

length of the small intestine. A small, shallow acute ulcer was found on the lesser curvature of the stomach, lacking however any evidence of induration or fibrosis. A few cc. of stringy, coffee-ground material, representative of altered blood, were present in the stomach. A small polyp (2 mm. in diameter) was found at the rectosigmoid junction. The uterus was enlarged by several, very large leiomyomas and the latter appeared to compress the rectum and lower portion of the sigmoid colon. The liver and spleen were quite firm and red, again presenting the usual appearances seen in cases of chronic passive congestion. The kidneys were of normal size although their surfaces were finely granular. The "flea-bitten" appearance associated with kidneys of focal embolic glomerulonephritis, so frequently encountered in cases of subacute bacterial endocarditis, was not observed.

DR. REINHARD: Would you comment again about the uterus? I'm a little disturbed because the history indicated the patient had had a subtotal hysterectomy.

DR. KRAUS: I noticed that too.

DR. STANLEY HARTROFT: Most of the questions presented by this case have already been

answered by Dr. Kraus. I will demonstrate some aspects of the microscopic examinations of the mitral valve, lungs, liver, kidney and pancreas. In sections of the mitral valve evidence of an acute inflammatory response can be seen in the center of the lesion which becomes acellular and hyaline at the edges. (Fig. 2.) In the region of ulceration with perforation many polymorphonuclear leucocytes as well as lymphocytes are present. In one of these sections stained by Gram's method, clumps of dark blue micrococci are present in small numbers. The entire lesion is absolutely characteristic of subacute bacterial endocarditis superimposed on a mitral valve scarred by previous rheumatic disease, although Aschoff bodies cannot now be demonstrated.

Throughout the lungs, the air spaces are reduced or even obliterated by a chronic fibrotic process diffusely thickening the alveolar walls. The alveoli are filled with hemosiderin-laden macrophages and the pigment was also demonstrable in the fibrotic areas and in walls of blood vessels. The latter frequently exhibit concentric or eccentric plaques of fibrous intimal thickening.

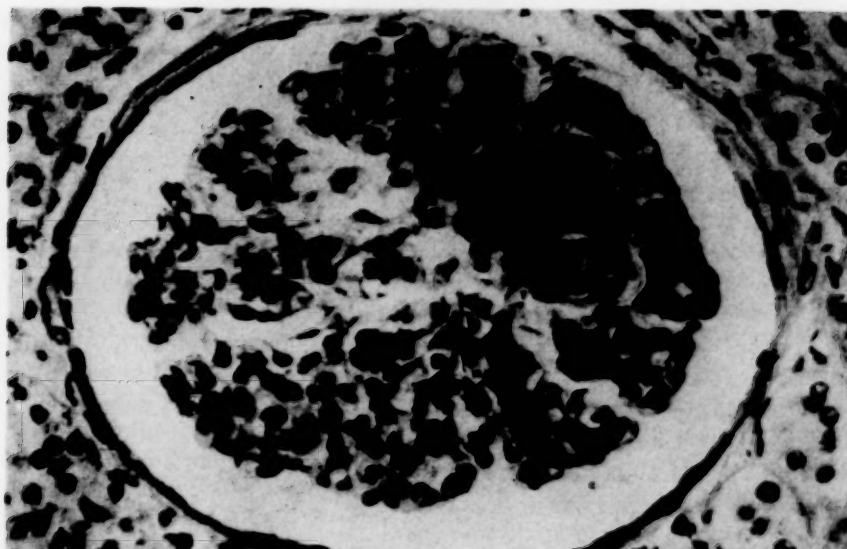


FIG. 3. Occasional glomeruli show a healing lobular necrosis without damage to the remaining lobules, consistent with a healing stage of focal embolic glomerulonephritis. Hematoxylin and eosin stain; original magnification, $\times 500$.

In microsections of the liver we again encounter the usual evidences of chronic passive congestion including a slight degree of fibrosis in centrilobular regions as well as atrophy of parenchymal cells in the same areas. Microscopically, the kidneys exhibited the typical focal lesions of atrophy and fibrosis associated with moderate nephrosclerosis. The walls of many arterioles were thickened and hyalinized, indicative of the patient's elevated blood pressure. In a few of the glomeruli, focal necrosis of individual glomerular lobules was encountered (Fig. 3) although the lesions are not typical of the usual form of focal embolic glomerulonephritis. A few groups of tubules stood out because of vacuolation of the epithelial mural cells. The pancreatic islets were diminished in number, size and intensity of beta cell granulation to a degree that would suggest a morphologic diagnosis of diabetes. Atrophy of acinar tissue at lobular margins again reminded us of the patient's state of chronic passive congestion. Microsections of the small gastric ulcer indicated its acute nature and in addition revealed the presence of monilia spores and mycelia on its surface. The ulcer may have accounted for the patient's tarry stools, but the anemia is more likely associated with the presence of subacute bacterial endocarditis.

The chief anatomic diagnoses were therefore as follows: Primary: chronic rheumatic endocarditis, slight, of mitral valve; chronic passive

congestion of the liver, lungs and spleen advanced with marked hemosiderin deposition in the lungs; chronic pneumonia, moderate, all lobes, with organization, most marked in the upper lobe of the left lung; calcium encrustation of elastica of pulmonary arteries; subacute bacterial endocarditis of anterior leaflet of the mitral valve with perforation of leaflet (Gram-positive cocci identified in section); acute congestion of the lungs, kidneys, and mucosa of gastrointestinal tract, moderate; ascites, serous, 500 ml.; hydrothorax, bilateral, serous, 100 ml.; subcutaneous edema of lower extremities, moderate; subacute peptic ulcer of mucosa of lesser curvature of stomach, with superficial growth of fungus, probably monilia; small amount of altered blood in stomach; linear erosions of mucosa of esophagus moderate; ecchymoses and petechiae of mucosa of stomach and small intestines; edema and ecchymoses of mucosa of urinary bladder; recent thrombi in pelvic veins; atelectasis of lungs, slight; (history of diabetes mellitus, years).

DR. HARFORD: I would like to ask if cultures were made of the valvular vegetation? It is sometimes difficult to distinguish the micrococcus and streptococcus on morphologic grounds and the streptococcus is by far the commonest cause of bacterial endocarditis.

DR. HARTROFT: Blood cultures were done, Dr. Harford but cultures were not made of the actual valve lesion.

Case Reports

Idiopathic Endomyocardial Necrosis*

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ENDOMYOCARDIAL necrosis is an uncommon condition of uncertain origin which has been reported under many names. It has not been established whether it is a single entity or whether it is a non-specific change seen under a variety of circumstances. The present report deals with a case of this type associated with striking changes within the pancreas. It is possible that these changes are related to one another, having a common but non-specific cause. It is the purpose of this article to draw attention to the alterations of pancreatic structure in the hope of stimulating a more intensive study of that organ in this disease state.

CASE REPORT

This twenty-nine year old Japanese woman was well until August, 1954, when she began to complain of fever and cough. She had had four pregnancies; the first three were uneventful, the fourth terminated spontaneously when the patient was six and one-half months pregnant. The infant weighed 3 pounds, 2 ounces at birth and died of pulmonary insufficiency forty-eight hours after delivery. In February, 1950, the patient complained of palpitation and physical examination revealed tachycardia, a fine tremor of the hands, moderate exophthalmos and a lid lag. The basal metabolic rate at this time was +30 per cent; the thyroid gland was moderately enlarged. Propylthiouracil was administered for five weeks, at which time it was discontinued because of the development of urticaria and angioneurotic edema. The patient refused surgery after symptoms decreased and her basal metabolic rate remained at normal levels. In addition she was seen on several occasions for the treatment of nasal allergy and sinusitis. She was well nourished and ate a balanced diet. Vitamin supplements had been given throughout her last pregnancy and the disease which followed it.

The patient's father was alive and well. Her mother had died of heart disease of unknown origin. One sister and three brothers were living and well. Two

sisters died in infancy. Her husband was living and well, two children were living and well, one child had died of acute leukemia, one child of pulmonary insufficiency in the neonatal period.

In early June, 1954, the patient was admitted to the hospital because of premature rupture of the membranes when she was six and one-half months pregnant. She had been threatening to abort for four months, and during this time she was given stilbestrol and progesterone. A routine x-ray of the chest was found to be within normal limits, although when viewed in retrospect there was thought to be a slight enlargement of the left side of the heart. In the latter part of June, the patient had an upper respiratory infection. She was seen by a physician in the middle of July, complaining of fever and cough of five days duration. Examination revealed the presence of rhonchi at the left base. The patient was treated with tetracycline, responded rapidly and was apparently well for one month. In August she began to complain of fatigue, cough and coryza. Transillumination of the sinuses at this time revealed clouding of the maxillary antrums. Penicillin was administered on three occasions with no improvement. Her fatigue persisted and a feeling of pressure developed in the epigastric region; she had occasional soft bowel movements (six times a day) and dyspnea on exertion. Physical examination revealed tachycardia, enlargement of the heart and basal rales. The blood pressure was 100/70. There was moderate exophthalmos. The patient was admitted to hospital for evaluation.

Laboratory findings: Urinalysis showed specific gravity 1.010, albumin trace, sugar negative, white blood cells 8 to 10. The white blood cell count was 9,000 per cu. mm. (neutrophils 62 per cent, lymphocytes 36 per cent, eosinophils 2 per cent), hemoglobin 13.1 gm. per cent, hematocrit 47. Feces showed 4+ occult blood in three specimens, was negative for ova and parasites; no eosinophils noted. The serologic test for syphilis was negative. Thymol turbidity was 4 units gamma globulin 7 units.

The patient was sent home where despite treatment with digitoxin her fatigue and shortness of breath increased. In the latter part of September pitting edema of the lower extremities and edema of the face

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and hands developed. She was readmitted to the hospital on September 24, 1954.

Physical examination at this time revealed the patient to be very apprehensive, short of breath at rest and cyanotic. There was obvious edema of the face and hands. The jugular veins were distended. The thyroid gland was barely palpable. The blood pressure was 110/90. The heart was enlarged to the left anterior axillary line. There were no murmurs or irregularities of rhythm. The second heart sound was reduplicated in the third left interspace. There were rales at both lung bases. The liver was enlarged four fingerbreadths below the right costal margin. The spleen was palpable one fingerbreadth below the costal margin. There was no gross ascites. The patient was afebrile on admission. Her resting pulse varied from 80 to 120. Her respiratory rate varied from 20 to 28. An electrocardiogram revealed absence of the R wave in lead 1 with the presence of an S wave. The T wave was low and upright in lead 1, but in leads 2 and 3 the ST segments were depressed. The ST segments were convex, with inverted T waves in these leads. A similar pattern was present in lead AVF. In the unipolar precordial leads the descending limb of the QRS complex was slurred and notched. The ST segments were depressed followed by inverted T waves in leads V₃ and V₆. An x-ray of the chest revealed a large heart with evidence of pulmonary congestion. Venous pressure was 260 mm. of water.

Laboratory findings: Urinalysis showed specific gravity 1.020, albumin trace, sugar negative, white blood cells 4 to 8 and red blood cells 8 to 10. The white blood cell count was 10,650 per cu. mm. (neutrophils 56 per cent, lymphocytes 38 per cent, monocytes 4 per cent, eosinophils 2 per cent). Hemoglobin was 14.6 gm. per cent, hematocrit 49. Blood chemistries were serum non-protein nitrogen 37 mg. per cent, sugar 107 mg. per cent, cholesterol 152 mg. per cent, albumin 3.3 gm. per cent, globulin 1.9 gm. per cent. The protein-bound iodine was 6.4 µg. per 100 cc. The serum alkaline phosphatase was 1.8 Bodansky units, icterus index 10, Van den Bergh direct negative, indirect 0.4 mg. per cent. Search of the peripheral blood and bone marrow for L.E. cells was negative. The bone marrow had a normal cellularity with a myelo-erythroid ratio of 2.4:1. There was slight lymphocytosis of the marrow.

The patient was digitalized with gradual disappearance of her edema. An x-ray of the chest on the fifteenth hospital day revealed a reduction of the cardiac shadow and disappearance of the pulmonary congestive changes. Subsequently, however, in spite of continued digitalis therapy, the patient's clinical condition again deteriorated. The heart appeared larger and fluoroscopic examination on the twenty-ninth hospital day revealed poor pulsation of the left cardiac border. A paradoxical pulse was noted. Aspiration of the pericardium yielded blood which clotted rapidly and had a xanthochromic serum. She was

again tapped the following day with similar findings. Following these procedures the patient improved to a slight extent. On the thirty-fifth hospital day the patient began to have four or five soft stools a day. Stool examination failed to show amebae. A low grade fever developed which on one occasion reached 100.8°F. At the same time she also complained of lethargy, nausea and headache. On the fortieth hospital day all medications were discontinued. Her edema rapidly reappeared and shortness of breath increased. On the forty-seventh hospital day she had a sudden feeling of precordial constriction and died in a few minutes.

NECROPSY FINDINGS

The body was that of a twenty-nine year old Japanese woman who was well nourished. The skin of the lower extremities pitted deeply on pressure; nailbeds were cyanotic; nipples were darker than usual; eyes were prominent; forearms were hairy. The pleural spaces were patent, each containing approximately 1,000 cc. of reddish brown fluid. The pericardial sac bulged before it was opened. When opened, the sac was found to be distended with reddish brown fluid. The abdominal cavity contained 500 cc. of clear straw-colored fluid. The liver edge was approximately 6 cm. below the costal margin at the lateral margin of the right rectus muscle.

The head was not examined due to limitation of the autopsy permission. Each lobe of the thyroid gland measured approximately 4 cm. in length. The outer surface was smoothly lobulated; cut surface showed no evidence of gross pathologic change. The lungs weighed 580 gm. Their pleurae were smooth. Present in the subpleural portions of both lower lobes and the right middle lobe were sharply circumscribed, dark red, wedge-shaped zones which varied from 2.5 cm. to 5.8 cm. in diameter. These zones were non-aerated and were elevated from the surrounding pulmonary tissue. The remainder of the lung parenchyma was tan in color and, although aerated, had a boggy consistency. On dissecting the branches of the pulmonary artery into the lung, occasional clumps of dark red material were noted within their lumens.

The heart weighed 410 gm. Epicardial fat was scanty in amount, and there were numerous ecchymoses and petechiae in the epicardium. These were most numerous in the atrioventricular sulcus and along the course of the left anterior descending coronary artery. The entire

endocardial surface of the right heart was smooth and shiny, the foramen ovale was closed, and the auricular appendage was patent. The tricuspid valve ring measured 11.5 cm. in circumference; pulmonic valve ring measured 7.2 cm. in circumference. The leaflets of both valves were thin and delicate. The right inflow tract measured 7.7 cm. in length, and right outflow tract measured 10.2 cm. in length. The pulmonary conus was prominent. The interventricular septum bulged towards the right. The entire endocardial surface of the left auricle was smooth and shiny. The auricular appendage was patent. The mitral ring measured 9.2 cm. in circumference, and its leaflets were thin, delicate and avascular. The chordae tendineae were thin and delicate. Present on the wall of the left ventricle was a mural thrombus which extended from the apex upwards for a distance of 8.2 cm., reaching to within 2.3 cm. of the atrioventricular sulcus. The thrombus extended onto the posterior one-third and the anterior edge of the interventricular septum. It had a sharply circumscribed edge and could be peeled with some difficulty from the underlying endocardium. The latter was greenish white in color and measured from 1 to 2 mm. in thickness. There were occasional small, white patches of endocardium, free of covering thrombus, over the endocardium of the interventricular septum. The papillary muscles were flattened. The wall of the left ventricle measured from 7 mm. to 1.2 cm. in thickness. The deeper portions of the clot were yellow-red in color. The myocardium of both ventricles and of the interventricular septum was flabbier than usual. The aortic ring measured 6 cm. in circumference. The leaflets were thin and delicate. The coronary ostia were patent, and the coronary arteries were patent as far as they may be traced. Their walls were soft, pliant and almost completely free of plaques. Those that were noted were very ill defined streaks which varied from 1 to 2 mm. in length and less than 1 mm. in diameter. The aorta retained almost all of its elasticity. Aside from occasional ill defined, yellow streaks adjacent to the intercostal muscles, the luminal surface was without interest. These streaks varied from 1 to 2 mm. in length.

The liver weighed 1,050 gm. The capsular surface was green in color after fixation in formalin. The hepatic markings were prominent (nutmeg liver). This change was not uniform throughout the liver, being most conspicuous in

the inferior and subcapsular aspects. The biliary tree was patent throughout. The pancreas was firmer than usual, buff colored and had an intact lobular pattern. It weighed 67 gm. The spleen weighed 160 gm. Its capsular surface was tense and purplish red. The cut surface was dark red and contained prominent follicles. Present within the lateral aspects was a wedge-shaped, sharply circumscribed, yellow zone measuring 1.5 cm. in width and 2 cm. in depth. The adrenal glands were symmetrical in size. The cortical portions measured 1 mm. in thickness and were dull brown. They contained occasional flecks of golden tissue. The medullary portions showed no gross evidence of pathologic change.

Each kidney weighed 160 gm. Present in the right kidney was a well defined zone where the cortex was golden yellow. Bordering the golden yellow zone was an area of the cortex which was dark red and had a hemorrhagic appearance. The involved area measured 2.4 cm. in its greatest width. Pelvic fat was somewhat increased in amount. The urinary tract, genital organs, gastrointestinal tract, parathyroid glands and musculoskeletal system showed no evidence of pathologic change.

MICROSCOPIC DESCRIPTION

Lungs. The alveolar spaces in the dark red areas were filled with red blood cells. The alveolar septa were necrotic. Present within the pulmonary arteries serving these portions of the lung were clumps of fibrin, neutrophils, fibroblasts and red blood cells. Protruding into the lumens of other vessels were rounded clumps of endothelial cells. In other areas the alveolar spaces and respiratory bronchioles were filled with clumps of fibrin, red blood cells, alveolar phagocytes, fibroblasts and collagen fibers. Within the intact portions of the lung bordering these zones, the alveolar spaces were uniform in size and contained hemosiderin-laden histiocytes. Their septa were thickened by dense connective tissue and were traversed by swollen capillaries. The bronchi were filled with mucus and red blood cells. The bronchial arteries and arterioles were greatly thickened in their intimal aspects so that their lumens were either greatly narrowed or obliterated. The epithelium of the bronchial glands contained occasional neutrophils. The pulmonary arterioles were focally thickened in their intimal aspects by dense, hyaline connective tissue. Present on the surface

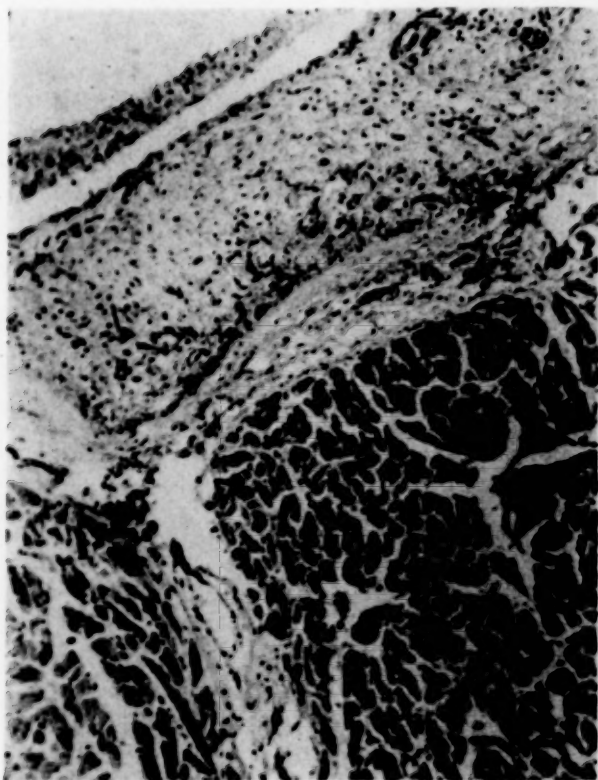


FIG. 1. Recent mural thrombus, left ventricle. Note intact myocardium at this site. Original magnification, $\times 120$.



FIG. 2. Area of recent myocardial necrosis, subendocardial aspects; left ventricle. Original magnification, $\times 265$.

of the pleura were collections of fibrin, red blood cells, histiocytes and nuclear fragments.

Right Heart. The muscle fibers of the ventricular myocardium appeared to contain clear vacuoles within them. There were numerous greatly distended capillaries within the interstitial tissue. The latter contained small areas where its collagen fibers had a pink-fibrinoid appearance. There was no cellular reaction adjacent to these zones. Dense collections of red blood cells were present within the epicardial fat of the atrioventricular sulcus.

Interventricular Septum. The muscle fibers were larger than usual. The septum contained patchy areas where the muscle fibers had been replaced by an edematous connective tissue composed of fibroblasts, lymphocytes and histiocytes. Also present were occasional minute areas where the muscle fibers had undergone necrosis. They had a pink-fibrinoid appearance and had lost their nuclei. The interstitial connective tissue bordering these zones contained monocytic cells.

Left Ventricle. The endocardium was covered by a thick layer of fibrin, red blood cells and nuclear fragments. (Fig. 1.) Deep to this was a thick granulation tissue containing dense col-

lections of histiocytes, lymphocytes, plasma cells, fibroblasts and collagen fibers. There were fairly well defined areas within the myocardium where the muscle fibers had a necrotic appearance. (Fig. 2.) The fibers were mixed with collections of neutrophils and nuclear fragments. In some areas the zones of necrosis blended with areas wherein the muscle fibers had been replaced by an edematous tissue rich in fibroblasts and myocytes. Present within the myocardium, and best seen in areas where there was extensive myocardial necrosis, were small vascular channels which contained clumps of fibrin, fibroblasts and endothelial cells within their lumens. The affected vessels appeared to be small arteries or arterioles. There were also small venous channels, the lumens of which were occluded by collections of fibroblasts. Some of these venous spaces communicated with the vascular spaces within the mural thrombus. (Fig. 3.)

Liver. The radial arrangement of the liver lobules was well preserved. In most areas the central veins and the central liver sinuses were greatly distended. Where this change was most conspicuous, the cord cells of the central portions of the lobules were widely separated and some



FIG. 3. Mural thrombus, left ventricle, with organization. Original magnification, $\times 45$.

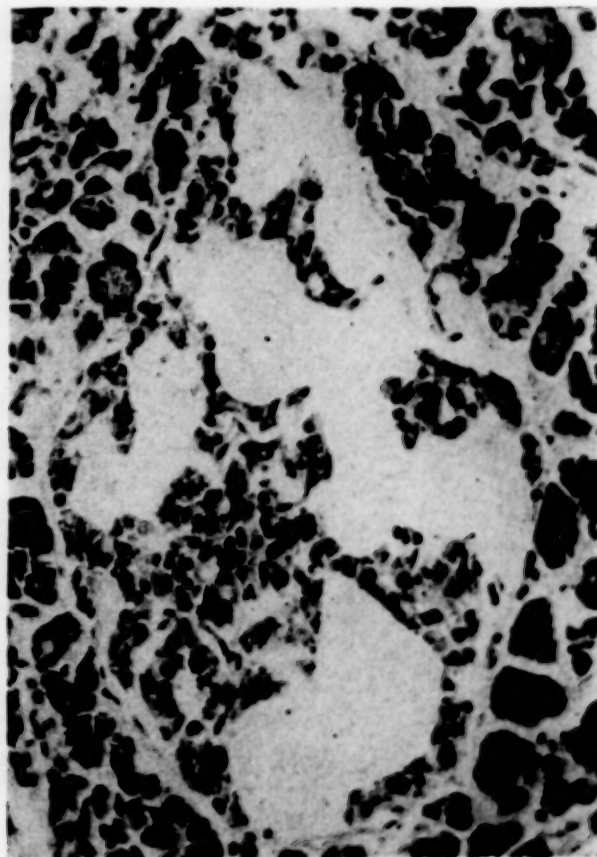


FIG. 4. Large, edematous islet; pancreas. Original magnification, $\times 265$.

had undergone necrosis. Neutrophils were arranged along the persisting reticulum.

Spleen. There was a sharply circumscribed area where the parenchyma was necrotic. A small artery serving this zone was occluded by collections of red blood cells, fibrin, neutrophils and nuclear fragments. The zone of necrosis was bordered by an intact parenchyma containing blood-filled sinuses. The follicles were indistinct. Some of the splenic veins were filled with an edematous connective tissue composed of fibrin, fibroblasts, red blood cells, histiocytes and small vascular channels.

Adrenal Glands. The cortical portions were much thinner than usual. The cells of the zona glomerulosa were shrunken from the reticulum. There was marked depletion of cytoplasmic lipid in all levels of the cortex. The fascicular and reticular zones were greatly diminished in volume. Present within the medullary portions and extending for variable distances into the cortical aspects were focal aggregations of lymphocytes, plasma cells, occasional histiocytes and red blood cells.

Pancreas. The neck, body and tail of the pancreas were similar in appearance. The islets were larger than usual (Fig. 4) and contained large vascular spaces which were filled with blood and pink-staining material. This islet enlargement was accentuated by a decrease in the volume of acinar tissue. (Fig. 5.) The acini were small and separated from one another by an edematous connective tissue containing plump fibroblasts, monocytes and dilated capillaries. The ducts were partially lined by clumps of squamous-like cells which protruded as globular masses into the duct lumens. (Figs. 6 and 7.) In some areas these clumps of cells were covered by flattened epithelial cells. This tissue pattern carries the implication that these cells are not of epithelial origin. It is the impression of the writer that they arise from subepithelial capillaries and represent a focal proliferation of endothelial cells. A few of the acini contained pink-fibrinoid material. The interlobular and peripancreatic fat contained areas of fat necrosis. These were surrounded by neutrophils and histiocytes.

Kidneys. One kidney contained an area of

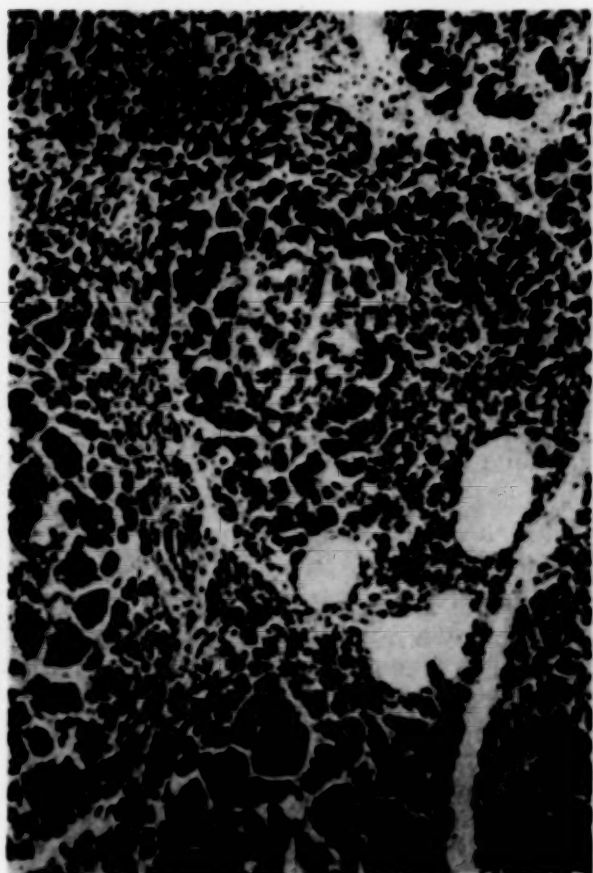


FIG. 5. Pancreas showing atrophy of acini. Note the halo effect caused by the relative preservation of acini adjacent to islets. Original magnification, $\times 45$.

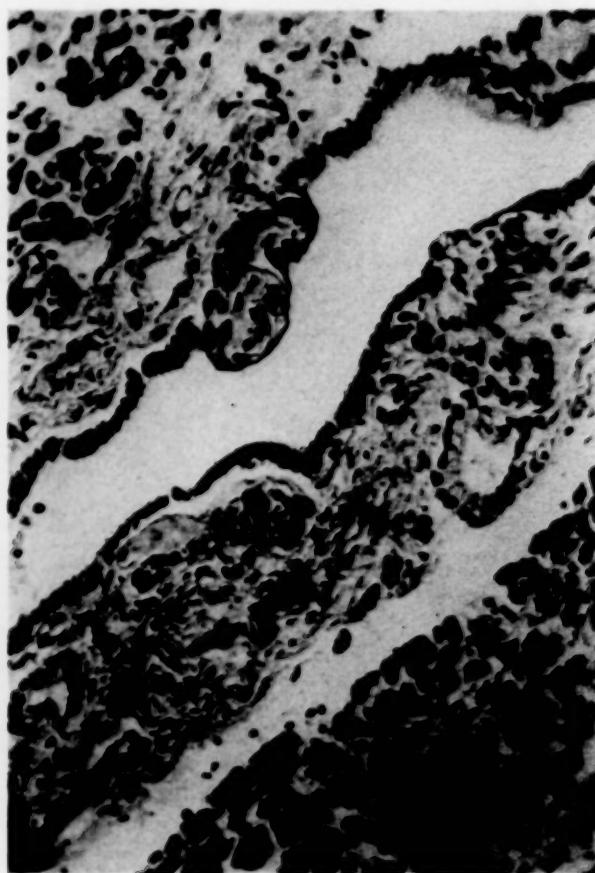


FIG. 6. Globular mass of subepithelial cells protruding into duct lumen. Early change showing intact epithelium stretched over the cell mass. Original magnification, $\times 265$.

cortical necrosis. The outlines of the cortical structures were preserved in this region. Dense collections of red blood cells were noted in the glomerular loops. Present within the capsule bordering the area were distended capillaries, plasma cells, lymphocytes and fibroblasts. The medulla deep to this region had viable tubules. There were several small arteries, the lumens of which were greatly narrowed by a thickening of the intima. This thickening had resulted from a proliferation of the endothelial lining cells and reduplication of the internal elastic lamina. The loops of Henle and collecting tubules contained numerous hyaline casts, focal collections of neutrophils and occasional red blood cells. Within the intact cortex the glomerular tufts were fairly well preserved. The capillaries of the interstitial tissue and the glomeruli were distended.

Sections were also taken of the breast, skeletal muscle, thymus, thyroid and parathyroid glands, lymph nodes, uterus, large intestine and bone marrow. These did not reveal any significant changes.

The slides and protocol in this case were sent to the Armed Forces Institute of Pathology for review. It was coded by that group as idiopathic cardiac hypertrophy with endomyocardial necrosis and fibrosis.

COMMENTS

Cardiac disease similar to that noted in this case has been reported by numerous authors in Africa,¹⁻⁴ Europe⁵ and America.⁶⁻⁸ By far the greatest number have been described among native Africans. It is unfortunate, however, that there is little uniformity among various observers as to the exact nature of the disease. An example of this diversity of opinion is as follows: Davies^{2a} has described endomyocardial fibrosis as one of the commonest causes of death due to heart disease in Uganda, British East Africa. Becker et al.¹ writing in South Africa in a paper on parietal endocardial thrombosis appear to include the East African cases in the same class as their own. The Uganda workers,^{2b,c} however,

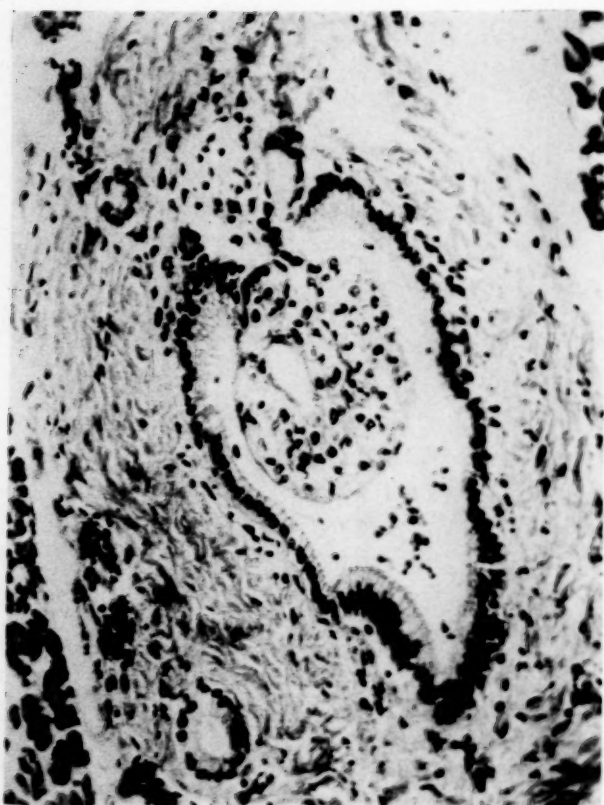


FIG. 7. Globular mass of subepithelial cells protruding into duct lumen. Note atrophy of covering epithelium and the numerous monocytic cells mixed with the cell mass. Original magnification, $\times 265$.

feel that Becker's group of cases is heterogeneous and that, although it may contain cases identical to the East African type, it is not representative of it. Thomas et al.⁶ compound the confusion. After surveying the African scene from America, they concluded that Becker's cases were identical with the East African cases but believed that Becker was not justified in including some of their own cases in this group. Williams, Ball and Davies^{2c} raise the question as to whether we are dealing with a pathologic entity or with an end-result common to several causes. They point out that there is a wide variety of possible causes of this cardiac disease, among which they number virus infection, allergy, collagenosis, toxins or malnutrition. It is also possible that two or more of these factors may work in concert to produce cardiac damage.

Any attempt to establish this entity as a systemic disease should include a search of other organs for commonly associated lesions. This point was made by Elster, Horn and Tuchman.⁸ These authors reviewed the work of Becker et al.¹ in which the disease was represented as a mani-

festation of diffuse collagenosis. The reviewers felt that the collagen degeneration was non-specific and limited to the subendocardium. They stated that collagen diseases are characteristically systemic in character and associated with a distinctive, although protean, clinical picture.

It is for this reason that the pancreatic changes in the present case are of particular interest, since these structural alterations have not been previously associated with this condition. These changes may be summarized as follows: (1) exocrine tissues: acinar depletion and acinar cell atrophy; focal proliferation of cells in the subepithelial aspects of the ducts; interacinar edema and infiltration with fibroblasts and monocytes; acute interstitial fat necrosis; (2) endocrine tissues: islet edema and enlargement.

In order to evaluate the importance of these changes in relation to endomyocardial necrosis, the writer requested the Armed Forces Institute of Pathology to review the pancreatic material in its cases of this disease.⁹ It was noted that of twelve cases, seven showed changes in the pancreas. Most of these consisted of focal necrosis of acinar tissue and fat necrosis. Sometimes ducts were plugged with secretions; and, in one case, calculi, interlobular fibrosis and inflammation were variables of this same pattern of pancreatitis. In one case numerous islets were noted, and in several instances there were occasional large islets. However, these were not more than one might see in any twelve cases selected at random for examination.

Changes in the exocrine tissues of the pancreas similar to these have been reported in several states. Selye¹⁰ noted characteristic changes after a number of alarm stimuli (formaldehyde, morphine, atropine, adrenaline, spinal shock, surgical shock, cold and exercise). These were seen during the alarm reaction stage. The gland lost its white color, becoming pink. The islets of Langerhans were readily distinguishable to the naked eye. Histologic sections revealed the acinar cells to have lost their secretory granules. They retained granules only in the immediate vicinity of the islets of Langerhans, forming an eosinophilic halo of almost normal excretory cells around the endocrine tissue accumulations. This striking halo-like arrangement was reproduced in the present case. The greatest degree of acinar atrophy and interacinar inflammation was noted at the peripheral portions of the lobules at the greatest distance from the islets.

Davies¹¹ reported acinar cell atrophy as an early change in kwashiorkor. Later he noted hyaline change in some cells and tubular dilatation, and periacinar, intralobular and peritubular fibrosis. There was also periductal fibrosis. The acinar tissue was broken up by the fibrosis and the lobular outlines were delineated by broad bands of fibrous tissue. In advanced cases the acinar tissue disappeared over wide areas. Is this pancreatic change secondary to adrenocortical exhaustion due to the combined effects of protein deficiency and intercurrent disease? It is of interest that this disease occurs in the same area where a form of endomyocardial fibrosis is particularly common. Higginson et al.⁴ have reported cases of heart disease, some similar to the present case, which are associated with the nutritional defects similar to those described in kwashiorkor. The natural diet of their patients is qualitatively inadequate. It is imbalanced in respect to amino acids, lacks animal protein, and the carbohydrate content is disproportionately large.

Islet enlargement has been reported in Addison's disease by Hinerman¹² and by Russfield.¹³ Occasionally the islands are large enough to suggest adenomatous hyperplasia. Sloper¹⁴ does not believe that Hinerman's claims of islet hyperplasia are valid, although he did note some islet adenomas in two cases of this disease. It is of interest that Davies felt that there was islet hypertrophy and possibly hyperplasia in kwashiorkor. Is this additional evidence of adrenocortical exhaustion in this disease?

The pancreatic changes so far described have been seen in pathologic states characterized by the alarm reaction phase of the general adaptation syndrome and by the end stages of adrenocortical exhaustion. It is of interest that the histologic appearance of the adrenal cortex in the present case was typical of the latter condition. In addition the patient had marked skin pigmentation not unlike that seen in Addison's disease.

The ductal changes seen in the present case were of particular interest to the writer. In view of the rather striking lesions in other segments of the gland, I assume, for want of a better explanation, that they all have a common cause. Small globular masses of cells, apparently arising from capillaries, appear in the subepithelial aspects. As they grow, they push the lining epithelium upwards until it becomes thinned. There is no epithelium over the larger elevations, and

here the cell masses are mixed with inflammatory elements (neutrophils and monocytes). It is probable that this change is not too uncommon, but rather it has been passed off as squamous metaplasia. I have made a superficial review of the cases of so-called collagen disease in my files and have found the same lesion in the case of a thirteen year old girl who died of rheumatic fever. This lesion was actually described and coded as squamous metaplasia. An extensive study of the pancreas in all disease states will be required before its true incidence is established.

I believe that the basic pattern of the pancreatic changes fits into the framework of the general adaptation syndrome. The failure to demonstrate a specific cause of the cardiac disease may rest upon the fact that none exists. One or more unfavorable stimuli working over a long period of time in susceptible individuals may account for the disease.

SUMMARY

1. A case is described in which endomyocardial necrosis was associated with pancreatitis. The pancreatic disease was characterized by islet enlargement, edema, peripheral acinar atrophy, interstitial inflammatory change, acute fat necrosis and focal proliferation of subepithelial cell masses within the ducts.

2. The pancreatic changes appear similar to those seen in adrenocortical failure and during the general adaptation syndrome.

3. The significance of the associated pancreatic and cardiac diseases is discussed.

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Occluding Thrombus of the Right Atrium*

Intermittent Tricuspid Occlusion in a Case of Atrial Infarction with Mural Thrombosis

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ALTHOUGH atrial mural thrombus formation is a common postmortem finding in all types of heart disease^{1,2} it is only rarely that such thrombi become of sufficient size or are so strategically located as to obstruct the associated valve and produce clinically recognizable physiologic disturbances. Occlusive or obstructive thrombi are usually of three types—ball thrombi, pedunculated thrombi, or so-called mass thrombi. With very rare exceptions, such thrombi have been described as occurring in the left atrium, most often in association with mitral stenosis.

Since the first description in 1814 by Wood³ there has been recurring interest in the dramatic clinical symptoms produced by occlusive thrombi. The majority of cases reported to date have been concerned with the effects of obstruction of the mitral valve and a small number of these have been diagnosed antemortem on the basis of criteria suggested in 1890 by von Ziemssen.⁴ Bozzolo in 1896 made the first antemortem diagnosis following von Ziemssen's criteria.⁵

The clinical picture of thrombotic occlusion of the tricuspid valve is much less well known, only three well documented cases have been reported to date. In one of these diagnosis was made antemortem and the findings consisted of a ball thrombus in association with rheumatic heart disease.⁶ The others were due, respectively, to a ball thrombus accompanying acute vegetative endocarditis⁷ and a pedunculated thrombus in a heart exhibiting coronary sclerosis and thromboangiitis obliterans.⁸

The present report is concerned with a description of the clinical syndrome produced by an occlusive thrombus of the right atrium resulting from infarction of the atrial wall. This thrombus was of proper size and location

to occlude intermittently the tricuspid orifice and produce a clinical syndrome sufficiently dramatic to make antemortem diagnosis possible. We were unable to find a previous clinical description of an occlusive thrombus complicating atrial infarction.

CASE REPORT

C. T. was an eighty-eight year old white man who was admitted to the Hunterdon Medical Center on October 24, 1953. He died on October 31, 1953. The patient was in a state of good health until two days before admission when, while standing in the street, he experienced sudden onset of substernal pain associated with dyspnea and weakness. He was seen by his family physician several hours later because this pain persisted. His blood pressure on examination was 120/80. There was no evidence of congestive failure and the ventricular rate was 80 at the apex. He was treated at home for two days with bed rest. When he was examined again by his family physician it was noted that his pulse rate, which had been 88 on the previous two days, had dropped to 44. There was no other change in his clinical picture.

The family physician reported that the patient had hypertension for the previous eleven years with occasional episodes of angina pectoris. For about the same period, he also had a duodenal ulcer with recurrent episodes of epigastric distress following meals; the pain had been relieved by food and antacids.

The system review did not reveal any other significant abnormalities.

Examination on admission revealed an acutely ill, elderly white man complaining of precordial pressure. There was slight dyspnea and slight cyanosis of the lips and nailbeds. Temperature was 97°F.; pulse 32; blood pressure 130/80; respirations 30. There were a few moist rales at both bases. Examination of the heart revealed the following: no point of maximal impulse could be palpated, the sounds were distant; the ventricular rate was regular at 40 beats per minute, a presystolic gallop rhythm was present. The aortic

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and pulmonic second sounds were equal. There was a loud, systolic grade 3 murmur at the apex. The neck veins were only slightly distended. The liver was not palpable. The abdomen was soft. There was no peripheral edema.

Initial laboratory data were as follows: Hemogram: hemoglobin 14 gm.; red blood cell count 4,770,000; white blood cell count 8,300; neutrophils 82 (78 segmented); lymphocytes 13; monocytes 5. Urinalysis: pH 5; specific gravity 1.024; trace of protein; sugar negative. The blood urea nitrogen was 12.6 mg. per cent. Electrocardiogram on admission revealed evidences of complete heart block with A-V dissociation, together with the changes of acute posterior wall myocardial infarction.

During the examination on admission striking blue-black cyanosis of the lips, nose, ear lobes, fingers and cheeks developed suddenly. Associated with this episode there was marked engorgement of the neck veins, restlessness and dyspnea, but no change in auscultation of the chest and no change in the cardiac rhythm. The patient was lying supine at the time. The cyanosis lasted about ten minutes and disappeared without the patient changing his position. Concomitantly the neck veins became flat and the air hunger disappeared.

During his hospital stay the patient was treated with bed rest, analgesics, oxygen and amphojel® for postprandial epigastric distress. Because of the history of chronic peptic ulcer, together with symptoms of epigastric distress, anticoagulants were not employed.

On the first hospital day coarse, wet rales developed in both bases together with Cheyne-Stokes respiration and diminution in the patient's sensorial acuity. He was digitalized with digoxin and maintained on 0.5 mg. per day of this medication.

During his hospital stay the most striking clinical feature consisted of recurrent episodes of intense cyanosis. Each day he had several attacks with a sudden increase in the degree of cyanosis to the point that his lips, earlobes, face and extremities appeared blue-black. Associated with this there was marked engorgement of the neck veins and veins of the upper extremities and there were disturbances in his sensorial state with either confusion and restlessness or somnolence. These episodes lasted from ten minutes to one-half hour, and ceased spontaneously with almost complete disappearance of cyanosis, great diminution in the engorgement of the veins, and return of the sensorium to a more normal state. At no time did the cardiac rhythm change nor did rales increase in the lungs. Changes in the patient's position did not appear to alter the episodes in any way. Peripheral pulses in upper and lower extremities and blood pressure readings were difficult to obtain during these episodes.

On the morning of the seventh hospital day the patient suddenly became cyanotic once more, but this

time he had several generalized convulsions followed by stupor with Cheyne-Stokes respirations and a change in pulse rate from 45 to 88. Blood pressure remained at 154/50. Electrocardiogram performed shortly after the onset of convulsions showed evidence of complete A-V block together with ventricular tachycardia from varying foci. (Fig. 1.) The patient was treated with oxygen, demerol® and aminophyllin. A repeat electrocardiogram showed complete heart block with disappearance of ventricular tachycardia. One hour after this episode the patient had a grand mal convulsion and died. Complete heart block was present on all serial electrocardiograms. No changes in the P-Q segment or PTA were noted at any time.

PATHOLOGIC FINDINGS

Gross. The exterior of the body was consonant with the stated age of eighty-eight years and presented no unusual features. The great serous cavities were normal. The heart weighed 500 gm., the enlargement being due principally to hypertrophy of the left ventricle. The most striking feature, however, was the marked dilatation of the right atrium and its appendage. Externally, these structures had a dark red granular appearance and their walls bulged outward rather prominently. (Fig. 1.) Cut section revealed this bulging to be due to a massive organizing thrombus which completely filled the appendage and extended out over the posterior wall of the atrium for a distance of 4 cm. (Fig. 1.) The cut surface of the atrial wall and appendage was very thin and presented a dark red, hemorrhagic, granular appearance, especially in the area occupied by the overlying thrombus. This blood clot was intimately adherent to the atrial endocardium. Its inner half had a pinkish gray appearance suggestive of organization, while the outer portions appeared to be of more recent origin. In view of the previous clinical impression of possible intermittent tricuspid occlusion, this feature was studied especially. The thrombus was believed to be strategically located and of sufficient size to have created an obstruction to the flow of blood from the right atrium to the right ventricle. The left atrium was completely negative and its appendage was patent. The right ventricular muscle averaged 4 mm. in thickness and showed no unusual alteration. The left ventricle averaged 18 mm. in thickness. Multiple sections of this muscle revealed an extensive area of recent infarction involving the basilar half of the posterior wall. This change was characterized by ill defined yellowish zones alternating with

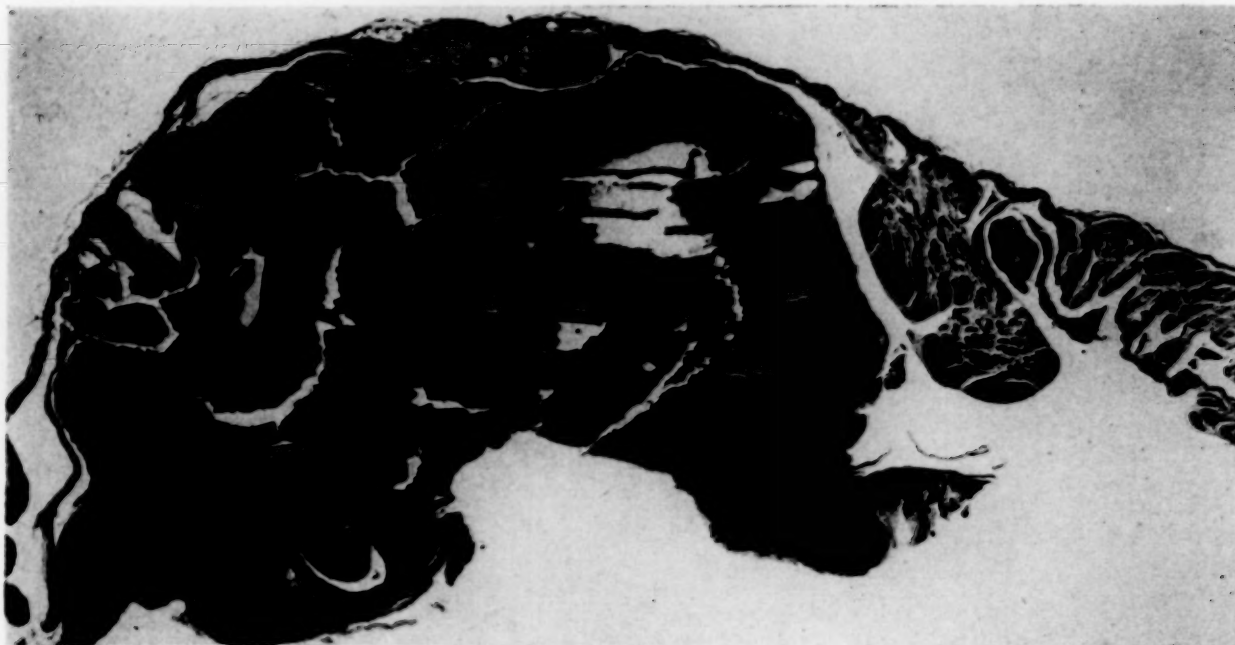


FIG. 1. Section of thinned out right atrial wall with the large adherent thrombus; hematoxylin and eosin, $\times 35$.

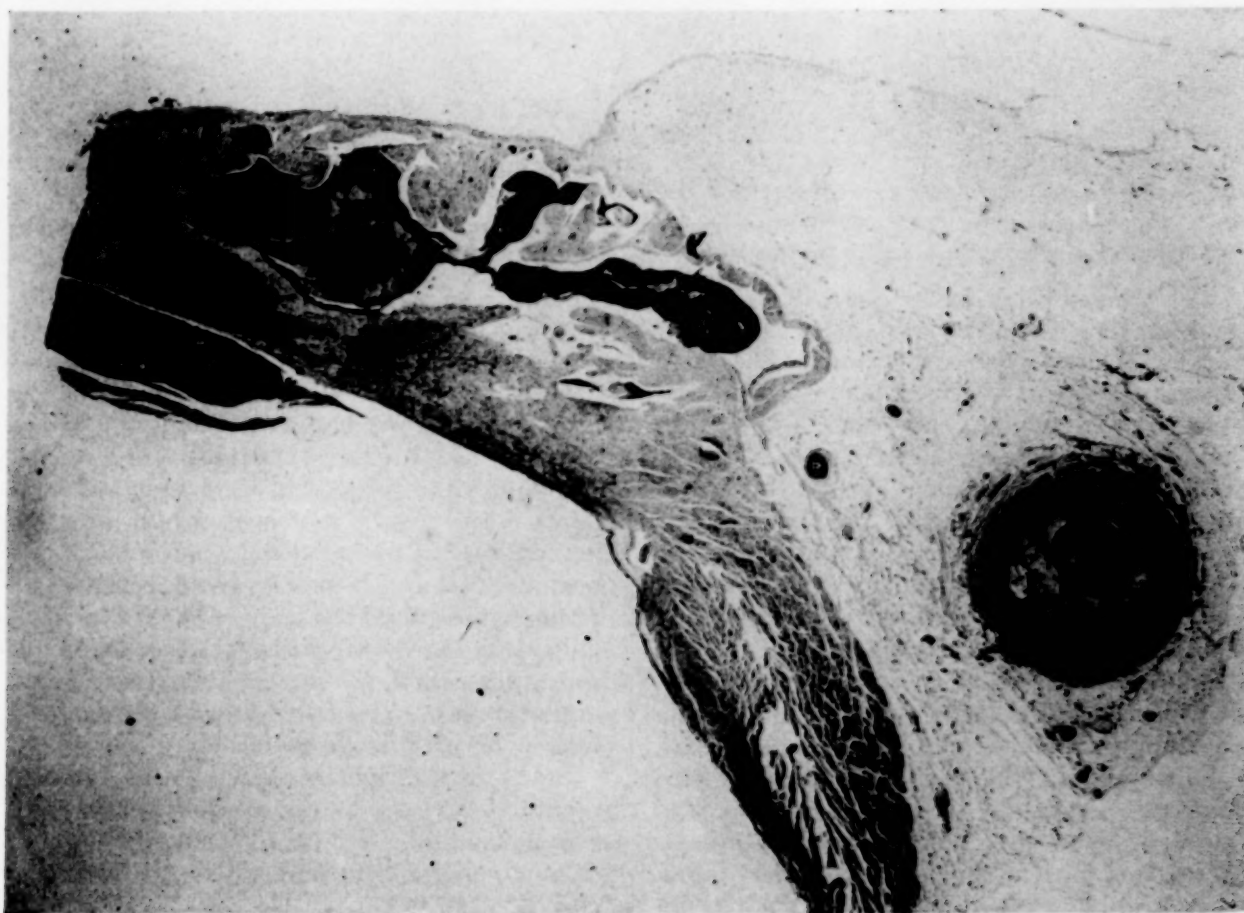


FIG. 2. Section through the thrombosed atherosclerotic right coronary artery. At the left can be seen the infarcted atrial muscle with the overlying mural thrombus; hematoxylin and eosin, $\times 35$.



FIG. 3. A higher power view of Figure 2, showing the smudgy atrial muscle fibers with interstitial edema and neutrophilic infiltration. Organization within the thrombus is visible; hematoxylin and eosin, $\times 100$.

hemorrhagic zones. The remainder of the left ventricular muscle was not unusual. The valve orifices were of average size and their leaflets were not remarkable. The coronary arteries were normal in distribution, medium in caliber and all three branches showed extensive atheromatous changes with calcification. The lumina of the left anterior descending and the left circumflex arteries were pinpoint in caliber at several points. The right coronary, in addition to this feature, contained an organizing thrombus which completely filled its lumen starting 1 cm. from its exit at the aorta and extending distalward approximately 1 cm. (Fig. 2.)

Examination of the rest of the organs revealed moderate congestion of the lungs, liver and spleen; a penetrating duodenal ulcer; a tubular adenoma of the left kidney; severe aortic atherosclerosis; moderate arterial and arteriolar nephrosclerosis. These gross findings were confirmed on histologic examination.

Microscopic Study. Section of the right atrium showed extensive infarction of muscle fibers, particularly in the subendocardial region. (Fig. 3.) Here muscle fibers had a pink amorphous appearance with loss of cross striations and nuclei. The interstitial tissue was edematous and contained large numbers of neutrophils. The free luminal edge of the atrial endocardium was covered by a thick thrombus which consisted of dense hyalin material with enmeshed neutrophils. (Fig. 3.) As the free edge of the thrombus was approached, it showed less evidence of organization and consisted largely of intact red cells along with fibrin.

Study of the right coronary at the point of occlusion revealed a dense pink hyalin mass completely filling its lumen. Moderate numbers of mononuclear cells and red blood cells were embedded in this mass. The vessel wall showed extensive atheromatous change characterized by concentric fibrous thickening of the intima,

destruction of the internal elastic membrane and the presence of large numbers of mononuclear cells in the media and adventitia. The media was severely compressed and the adventitia was thickened.

Section of the left ventricular muscle showed the same acute changes of infarction that were found in the right atrium.

Final Cardiac Pathologic Diagnoses. (1) Occlusion, recent, right coronary artery; (2) infarct, fresh, right atrium and posterior wall left ventricle; and (3) thrombus, massive, right atrium with partial tricuspid valve occlusion.

COMMENTS

There have been several excellent reviews in the literature of the clinical and pathologic features of ball-valve and other types of occlusive thrombi of the left atrium. The reader is referred to Abramson's review⁹ and to the more recent compilations of Evans,¹⁰ Evans and Benson,¹¹ Read et al.⁸ and Radding.⁷

The clinical features of occlusion of the mitral valve by thrombi in the left atrium have emerged from the clinical description of von Ziemssen,⁴ later supplemented by Bozzolo⁵ and Battistini¹² who made the first antemortem diagnoses. These authors suggested that the diagnosis of occlusive thrombi in the left atrium should be considered in a patient with mitral stenosis in whom signs of cyanosis and dyspnea developed together with diminution or absence of peripheral pulses, often with gangrene of the extremities. Elson¹³ added to this picture the important modality of intermittency of the cyanosis and of loss of the peripheral pulsations of the upper and lower extremities. Recently, Evans and Benson¹¹ have emphasized that similar clinical manifestations may be produced by adherent or pedunculated thrombi which do not satisfy the criteria set up for ball-valve thrombi (Welch¹⁴). They prefer the term "mass thrombus" which they apply to "any large thrombus, free or attached, occupying the greater part of the left auricle, as well as any small thrombus, that, by reason of its proximity to the mitral valve may cause obstruction to the flow of blood through the mitral orifice."¹¹

In contrast with the attention given in the literature to the clinical and pathologic aspects of occluding thrombi of the left atrium, we were able to find only three well authenticated, autopsied cases involving obstruction of the tricuspid valve. The first case reported was that

of Wright, Flynn and Druet⁶ in which a ball thrombus was observed in the right atrium in the presence of rheumatic heart disease and mitral stenosis. These observers were able to make the antemortem diagnosis in a patient with the clinical features of rheumatic heart disease in whom dusky cyanosis, dilated, pulsating neck veins and marked dyspnea developed. They emphasized the variations in intensity of the syndrome within short periods of time. They also found signs of tricuspid insufficiency, enlargement of the right heart and a changing cardiac silhouette on x-ray.

Radding⁷ reported a case diagnosed at post-mortem examination exhibiting a ball thrombus in the right auricle associated with acute vegetative endocarditis due to Friedländer's bacillus. The clinical features were not very suggestive except for air hunger, chest pain and sudden death.

The most recent case is that of Read et al.⁸ who report the first instance of a pedunculated thrombus in the right atrium acting as an occluding thrombus in a heart with coronary sclerosis and thromboangiitis obliterans. The striking clinical features were repeated episodes of air hunger, cyanosis, chest pain and transient loss of consciousness with feeble peripheral pulses and drop in blood pressure. These episodes could be precipitated by changing the patient's position in bed. The authors were impressed by the absence of rales during the episodes of dyspnea—an impressive finding in our own case.

Macleod¹⁵ in 1883 reported the case of a twenty-seven year old man with cholera who died following symptoms of convulsions, cyanosis and air hunger. A movable clot "half again as large as a walnut" was found overlying the tricuspid orifice. This case merits consideration, however, since it describes, although briefly, symptoms and autopsy findings suggestive of tricuspid occlusion. Certainly the triad of cyanosis, air hunger and convulsions described by Macleod recurs in the other three cases in the literature and in our own.

In 1945 Mahaim¹⁶ published a very extensive review of tumors and polyps of the heart. He was able to document thirty-seven cases of obstruction of the tricuspid valve at postmortem examination, only five of which could be considered thrombotic in origin. He very critically scrutinized the clinical aspects of these cases. The most frequent findings were dyspnea, cough, edema and occasional episodes of syn-

cope. Cyanosis was frequent but intermittency was not commented upon. Mahaim concluded that no consistent clinical syndrome was produced by tricuspid valve obstruction which was sufficiently reliable to be of aid in antemortem diagnosis. This applied also to the cases which were due to neoplasms occluding the tricuspid valve.

The clinical diagnosis, or at least suspicion of the existence of a tumor or thrombus producing obstruction of the mitral or tricuspid valves, has become of practical importance since the demonstration that such lesions can be successfully operated upon.¹⁷ The manifestations of an atrial tumor or thrombus would be the same and differentiation of little importance since surgical removal would be advisable in either case. Goldberg and Steinberg¹⁸ have emphasized the value of angiocardiology in the delineation of atrial tumors and suggest that ball thrombi would probably be demonstrable by this method as well. Clinical recognition of the possibility of valvular obstruction followed by angiocardiology should prove most valuable in the detection of these lesions.

There appears to be considerable overlap in the clinical manifestations of obstruction of the mitral or tricuspid valves. Dyspnea, cyanosis, signs of congestive heart failure, chest pain, cough, convulsions and intermittency of these symptoms associated with changes in the patient's position are shared by both types of obstruction. Mitral valve obstruction should be suspected when there is evidence of disturbances in peripheral circulation with absence of pulses in the extremities or gangrene of the toes, fingers or nose tip. When the remainder of the clinical features suggest rheumatic heart disease and mitral stenosis, the valve obstruction will most likely be due to thrombus.¹⁹ In the absence of such signs the possibility of tumor would be uppermost although thrombi have been reported in the absence of rheumatic heart disease.²⁰

Tricuspid obstruction, on the other hand, appears more probable when the signs of interference with right heart inflow predominate, such as marked engorgement with or without pulsation of the veins in the neck and upper extremities. Also of considerable interest is the presence of marked air hunger in the relative absence of rales in the lungs. These signs were striking in the cases reported by Wright et al.⁶ and Read et al.⁸ as well as in the present case. The diagnosis should also be considered in all

patients with so-called right-sided failure in which the pathogenesis is questionable.

Another interesting aspect of the case reported here is the production of an occluding thrombus as a consequence of atrial myocardial infarction. The high incidence of atrial mural thrombus formation in atrial infarction has been emphasized in recent studies of Cushing et al.,²¹ Soderstrom²² and Wartman and Hellerstein.²³ Despite this fact, a careful review of the clinical features of these cases (thirty-one of Cushing et al., forty-six of Soderstrom) and of others, failed to reveal any in which the atrial thrombus resulted in occlusion of either the tricuspid or mitral valve.

The attempts in most studies to reconstruct a suggestive picture of atrial infarction have not been successful since the signs of the associated ventricular infarct usually take precedence. Following the suggestion of Langendorf in 1939,²⁴ Hellerstein²⁵ in 1948 was able to make the diagnosis of atrial infarct on the basis of changes in the P-Q segment. In our case these changes did not occur but we were able to make the antemortem diagnosis on the basis of the signs produced by the associated thrombus. In view of the high incidence of thrombosis with atrial infarcts, we would like to suggest that the syndrome we have described may be useful in detection of this lesion.

SUMMARY

(1) A case is presented of atrial infarction with mural thrombus formation producing the syndrome of tricuspid valve occlusion by virtue of its size and position.

(2) The clinical syndrome produced was sufficiently striking so that antemortem diagnosis of both lesions was possible.

(3) Only three previous cases of occluding thrombi of the right atrium have been reported, none in association with atrial infarction.

(4) The clinical pictures of tricuspid and mitral valve occlusion are contrasted and their increasing practical importance is emphasized.

ADDENDUM

Since submitting this paper, an additional case of thrombus of the right atrium with tricuspid occlusion, which occurred in a patient with rheumatic aortic stenosis, has been reported by E. Frommer (*British Heart Journal*, January 1956). This paper describes symptoms similar to those in the present case. Dr. Frommer also refers to

two cases in the South American Literature (Moia et al. and Romana).

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Salt-losing Nephritis with Fixed Urinary Composition*

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ALTHOUGH the salt-losing tendencies of chronic renal disease have been emphasized, few cases have been reported demonstrating marked failure of the renal tubule to dilute the urinary sodium.¹⁻¹⁰ This case is presented to contribute additional clinical observations to the literature and to report on the uniformity of urinary electrolyte composition in this condition.

CASE REPORT

R. C., a thirty-seven year old white man, was admitted to the Medical Service of Brown Hospital on December 17, 1953. For approximately twelve years this patient had experienced mild intermittent epigastric pain which usually occurred after eating. He had received ulcer therapy (type and duration unknown) but had had no relief. Nine months prior to admission he noted mild weakness, malaise and shortness of breath on exertion. Three months later progression of these symptoms forced the patient to stop work as a gardener. At that time he also noted intermittent nausea with occasional postcibal emesis. Five months before admission the patient began to experience tingling and cramping in his arms and legs. A mild craving developed for salt which relieved these latter symptoms. Relief also followed food ingestion. With an unknown amount of weight loss and with further progression of his weakness and shortness of breath, he was admitted first to the Medical Service of the Cincinnati General Hospital on September 18, 1953. Here a diagnosis of chronic nephritis with salt-losing tendency was made. The patient was maintained on a regimen of high salt and fluid intake and was transferred to Brown Hospital for chronic care.

Approximately ten months prior to admission the patient had contracted gonorrhea which was successfully treated with penicillin. He had noted nocturia for six months before admission but no dysuria or dark urine. To his knowledge he never had had albuminuria, previous renal disease or hypertension. There was no history of scarlet fever. A system review was

non-contributory. The patient was not aware of any changes in skin coloration.

On admission physical examination revealed a thin white man who appeared chronically ill. He was oriented but responded sluggishly. The body temperature and pulse rate were normal; the blood pressure was 120/80. The skin was a sallow brown hue. Hydration appeared normal. Examination of the ears, nose and throat revealed no abnormalities. The conjunctivas were pale. Fundusoscopic examination revealed normal discs and vessels without extravasation or deposit. The neck was normal. The lungs were clear to percussion and auscultation. The heart was not enlarged and a normal sinus rhythm with a grade 1 apical systolic murmur was heard. Abdominal examination revealed mild epigastric tenderness without spasm. No masses or organs were palpable. The extremities appeared normal and neurologic examination was unremarkable.

Laboratory studies made during the patient's course in the two hospitals revealed a hemoglobin varying from 8.0 to 10.1 gm. per cent and a white count of 5,600 to 11,400 cells per cu. mm. with a normal differential count. The urine was usually acid with the pH approaching 7.0 terminally. The specific gravity ranged from 1.005 to 1.013. Of twenty-three specimens examined for albumin twenty-one were either negative or contained a trace; on two occasions a 2 plus albumin was observed when the patient was edematous from excessive sodium input. Frequent examinations of the sediment revealed no casts or cells except terminally when a few white blood cells were found after catheter drainage had been performed for a prolonged period. Sugar and acetone were never present. Urine cultures were negative. Phenolsulfonphthalein excretion was less than 10 per cent in two hours.

The blood urea nitrogen concentration ranged from 61 to 200 mg. per cent and was 114 mg. per cent at the time of death. The blood creatinine concentration was 9.2 mg. per cent on admission and rose to 17.1 mg. per cent terminally. The serum sodium concentration ranged from 120 to 145 mEq./L., that of chloride from 79 to 103 mEq./L., and that of potassium from 3.3 to

* From the Department of Medicine, University of Cincinnati College of Medicine, and the Medical Service of Brown Hospital, Veteran's Administration Center, Dayton, Ohio. Aided in part by a grant from the Cincinnati Heart Association.

5.2 mEq./L. The serum carbon dioxide content varied from 19 to 28 mEq./L. and was once 11 mEq./L. following excessive salt intake. The serum calcium concentration ranged from 8.9 to 10.3 mg. per cent, the serum phosphorus concentration from 3.0 to 8.8 mg. per cent. The serum acid and alkaline phosphatases were 0.3 and 1.2 Bodansky units, respectively. The serum albumin concentration was 3.3 gm. per cent, serum globulin 2.6 gm. per cent and serum cholesterol 176 mg. per cent. Two fasting blood sugar determinations were 112 and 122 mg. per cent. The Kahn serologic test was negative.

Roentgen examinations of the chest and long bones were normal. The electrocardiogram was normal. Gastric analysis showed no free hydrochloric acid after histamine stimulation. Liver function tests were normal. Examination of the cerebrospinal fluid revealed normal pressure, no cells and a protein content of 44 mg. per cent. The blood retained 74.1 per cent of injected congo red dye.

The patient was maintained most comfortably on a low protein diet with high fluid intake and a daily intake of sodium equivalent to 12 to 18 gm. of sodium chloride and 7.5 gm. of sodium bicarbonate. Decrease of sodium below the equivalent of 9 gm. of salt daily resulted in weakness and cramping, whereas an increase above 40 gm. a day resulted in oliguria and edema. At no time did the patient's blood pressure rise above 130/80. The ocular fundi remained normal in appearance. During the latter months of the patient's life evidence of a left peroneal neuritis with sensory and motor disturbance developed. Following the onset of uremic coma, the patient died on March 10, 1954.

Autopsy was performed ten hours postmortem. With the exception of the kidneys, the only significant pathologic findings were concentric hypertrophy of the heart and acute passive congestion of the lungs. The kidneys were small, weighing approximately 100 gm. each. In the upper pole of the right kidney there was a cyst measuring 2.5 to 3.0 cm. in diameter. The capsules which were stripped with difficulty revealed pale pink-gray cortices, both finely and coarsely granular. Cut sections of the kidneys revealed the corticomedullary boundaries to be obliterated. Multiple small cysts in both cortices and medullae were noted. The renal pelves were small with smooth white mucosal linings.

Microscopic examination of the kidneys showed the glomeruli in various stages of hyalinization. A few glomeruli demonstrated some thinning of the capillary walls and periglomerular fibrosis. In both the cortex and medulla there was marked interstitial fibrosis with focal and diffuse lymphocytic and histiocytic infiltrate. The arteriolar walls were thickened and hyalinized. There was no evidence of arteriolar necrosis or arteriolitis. The appearance of the kidneys was considered by the pathologist to be compatible with that of chronic pyelonephritis.

JANUARY, 1957

OBSERVATIONS

Balance studies were made during two periods of salt restriction. Data concerning sodium intake and urinary composition are listed in Table 1. A twenty-four hour aliquot of the low sodium diet used contained 24 mEq. of sodium by analysis.

In the first study the patient was placed on the low sodium diet for eight days and allowed salt by tablets as desired to achieve a sense of well-being. During this period his weight remained relatively constant. Although the sodium intake was not accurately measured, the daily urinary output ranging from 322 to 432 mEq. suggests that a daily intake of approximately 400 mEq. was most satisfying to the patient. On the ninth day his daily intake of sodium was decreased to less than 200 mEq. and at the end of the next day he noted mild abdominal and leg cramps. The patient continued in probable minimal negative salt balance to the fourteenth day when, due to a worsening of his cramps, he received 536 mEq. of sodium parenterally with immediate relief. On the fifteenth day his daily intake of sodium was limited to 71 mEq. The next day the patient again noted mild cramping. Three days later nausea and vomiting ensued followed by oliguria and eventual hypotension and salt therapy was reinstituted. At the time his serum sodium had dropped to 132 mEq./L. Again it will be noted that relatively little salt was lost before symptoms ensued.

During this period of study the urinary sodium concentration remained within narrow limits (95 to 124 mEq./L.) regardless of whether salt intake was excessive, moderate or restricted to the point of oliguria and hypotension. The concentrations of potassium, chloride, phosphorus and total solutes also remained relatively constant. Unfortunately, specimens from the fourteenth through the twentieth days were lost before concentrations other than sodium could be determined.

In the second study the effects of desoxycorticosterone acetate (DOCA) on mineral balance were investigated. During an eight-day control period with an intake of 409 mEq. of sodium daily, the patient remained approximately in sodium balance and symptom-free. His intake was then reduced to 89 mEq. daily and he received 10 mg. of DOCA intramuscularly. On the second day mild cramping occurred. Two days later nausea and vomiting occurred, followed by oliguria and hypotension,

TABLE I.
 URINARY COMPOSITION DURING SALT RESTRICTION

Day	Na Input (mEq./day)	Symptoms	Blood Urea Nitrogen (mg. %)	Serum Na (mEq./L.)	Urine					
					Volume (cc./day)	Na (mEq./L.)	Cl (mEq./L.)	K (mEq./L.)	P (mg. %)	Total Solutes mOsm./L.
Study I										
1	Low sodium diet (24 mEq.)	None	134	143	3,695	110	104	14.9	9.6	425
2	Same plus salt tablets ad lib.				3,525	117	108	16.3	8.4	554
3	Same plus salt tablets ad lib.				2,750	117	106	14.9	9.1	565
4	Same plus salt tablets ad lib.				3,655	117	109	13.8	9.1	554
5	Same plus salt tablets ad lib.				3,755	115	111	13.3	8.4	532
6	Same plus salt tablets ad lib.				3,230	110	110	11.4	8.1	441
7	Same plus salt tablets ad lib.				3,410	124	110	9.9	6.8	489
8	Same plus salt tablets ad lib.		94	141	3,365	119	110	9.3	6.6	468
9	200		96	136	2,100	115	106	11.3	7.4	467
10	200	Cramps			1,860	101	96	14.3	8.0	452
11	200	Cramps			2,420	113	103	12.4	7.1	495
12	200	Cramps			1,975	95	90	17.0	9.8	441
13	200	Cramps			1,425	98	92	17.2	9.8	462
14	536	None	92		2,265	104				
15	71				2,455	113				
16	71	Cramps			1,790	119				
17	71	Cramps			1,165	114				
18	71	Cramps			1,440	111				
19	71	Vomiting			660	109				
20	71	Hypotensive	82	132	510	119				
Study II										
1	409	None			3,880	121	110	11.3	3.6	441
2	409				4,110	119	110	11.9	4.7	431
3	409				6,290	119	112		7.2	420
4	409		64	132	1,630	120	112	8.7	7.8	358
5	409				3,900	116	110	10.6	9.5	366
6	409				2,740	109	108		10.6	375
7	409				2,320	110	102	13.9	10.9	415
8	409				3,950	116	101	11.7	15.6	372
9	89 mEq. plus 10 mg. DOCA	Cramps	82	136	1,725	116	90	24.8	14.1	484
10	DOCA daily	Cramps			1,740	120	82	23.4	23.0	484
11	DOCA daily	Cramps			2,170	112	81	24.8	18.0	495
12	DOCA daily	Vomiting			870	114	78	27.4	17.3	506
13	DOCA daily	Hypotensive	136	130	560	125	73	33.8	14.5	506

and the patient was put back on a high sodium intake. A loss of approximately 270 mEq. of sodium resulted in subjective symptoms and an additional 150 mEq. loss resulted in oliguria and hypotension.

Again the urinary sodium concentration remained quite constant during the control and DOCA periods. However, during administration of DOCA there was a decrease in chloride and an increase in potassium and total solute concentrations. Although these changes were small they appear to be significant when compared to those before the DOCA period. Whether they were due to administration of DOCA or to the degree of sodium depletion unfortunately cannot be determined. There was a slow rise in phosphorus concentration over the whole period which appeared unrelated to the DOCA.

In Figure 1 are shown the relations of daily urine volume to total solute and sodium loads.

Both relations are linear and significant. However, the correlation of flow and sodium load ($R = 0.99$) is significantly greater than that of flow and total load ($R = 0.91$, $P < 0.01$).

In both periods of salt depletion there was some diminution of the serum sodium concentration. However, no marked decrease was found as reported by others.¹⁰

COMMENTS

The clinical characteristics of salt-losing nephritis have been reviewed by others.^{6,8} The present case adheres closely to the syndrome in presenting normal blood pressure, absence of changes in the ocular fundi and abnormality of skin pigmentation. However, no description of an accompanying peripheral neuritis was found in the previous reports. The lack of response to DOCA is also in keeping with other reports in which not only DOCA^{2-5,7-9} but

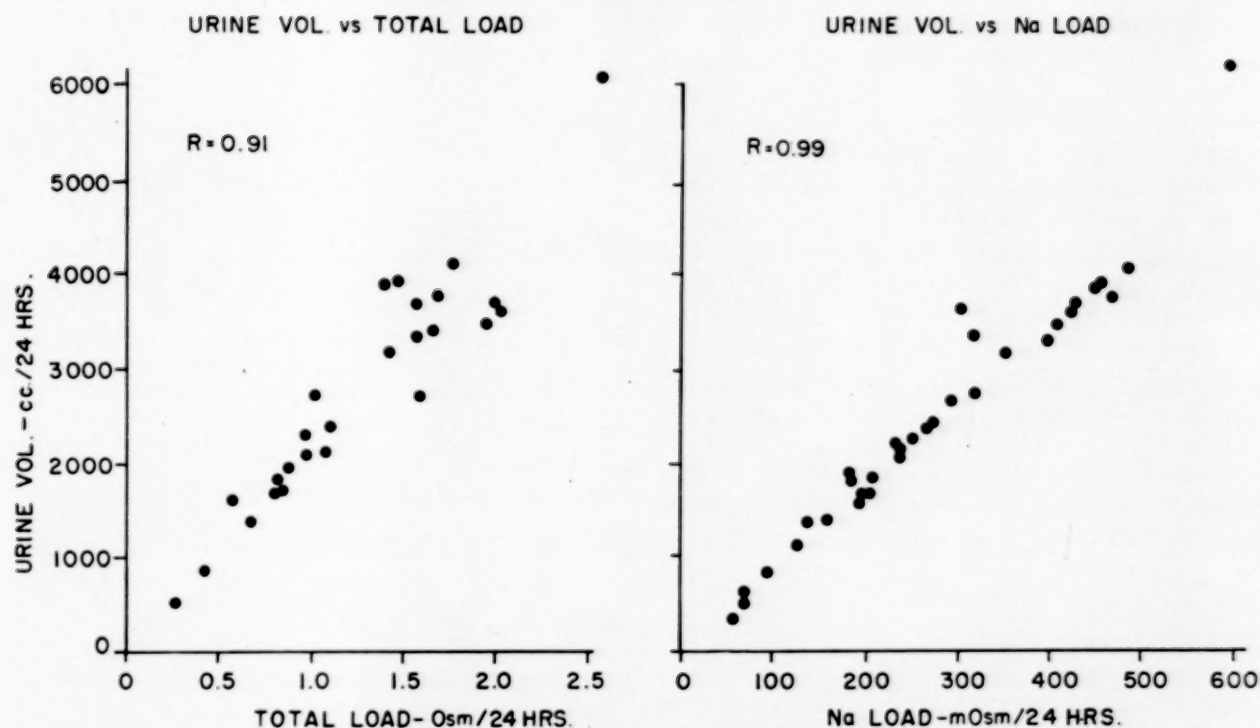


FIG. 1. The relations of urine volume and total and sodium loads.

adrenocortical extract^{2,7} and cortisone⁷ were reported to be ineffective. As there is evidence that aldosterone is already being produced in increased amount in this syndrome, one would not necessarily expect a response to exogenous hormone.¹¹

On histologic study the renal lesion was compatible with that of chronic pyelonephritis. This type of lesion has occurred most frequently in the limited number of cases reported.¹² In addition the renal cysts noted in this patient were prevalent in the other patients. In two of the reported instances the salt-losing state developed as part of the "milk and alkali" syndrome,^{5,10} and in another there was a history of ulcer therapy with renal calcinosis being found at necropsy.⁴ It is not clear what role the ulcer therapy may have played in the development of pyelonephritis in the current case.

Although isostenuria was expected in this condition, the observation of such narrow limits of electrolyte concentration was surprising. According to current concepts of renal physiology, urine flow and composition are dependent in the main on glomerular filtration and selective reabsorption. If these concepts are correct in this patient there must have been major derangements in sodium and chloride reabsorption. However, the site of these derange-

ments and the reason for fixation of the concentrations at levels below those of plasma are unknown. That the tubular secretion of hydrogen in exchange for sodium ions¹³ remained intact is evident from the maintenance of alkali reserve. That defective proximal tubular reabsorption of sodium with oversaturation of the distal tubule might have occurred is suggestive from the kaliuretic effect of the DOCA.^{14,15} Whether or not the presumptive site of final sodium reabsorption¹⁶ was disturbed cannot be ascertained. Also according to current concepts, in conditions of solute diuresis the flow is related to total load. In the present patient a significant relation was present but the correlation of flow and sodium load was greater. However, this relation is somewhat teleologic in that the narrow range of sodium concentration would of necessity produce an almost perfect correlation and dependency cannot necessarily be inferred. Nevertheless, despite wide variation in sodium intake the urinary sodium and its corresponding anion accounted for half of the total load and may have influenced flow. The situation could be considered analogous to that of uncontrolled diabetes mellitus in which glucose becomes the major factor in determining total load and flow.¹⁷

Some of these obscurities might be resolved in view of the recent observations of Chinard

and Enns.¹⁸ In contrast to current renal concepts, these investigators have presented evidence that part of the urinary water and sodium load may bypass the glomerulus and be secreted distally in the nephron. If these findings are correct, there may have been in this patient a defect in this secretory mechanism in which excessive sodium was secreted in fixed concentration, and this secretion was dependent on sodium intake. This mechanism would be considerably simpler in the production of a constant load than that of filtration and reabsorption alone which would entail marked flexibility of tubular reabsorptive capacity.

It is of interest also that relatively little loss of sodium led to symptoms of salt depletion. The patient resembled the subject with adrenal insufficiency in this respect and was in contrast to experimentally induced salt-depleted normal man, in whom considerably more sodium may be lost without deleterious effect.¹⁹ There is evidence that bone may act as a labile reservoir of sodium and may contribute sodium to the extracellular space in acute sodium deficiency.²⁰ In this patient the bone reservoir might conceivably have been deficient in sodium.

Finally, the consistency of the urinary load is significant in regard to therapy. In such a patient ideal treatment should be guided by a knowledge of the limits of tubular dilution and concentration of substances to be excreted. Following establishment of an optimal daily urinary output of water and urea, the input of electrolytes should be adjusted in the diet so that imbalances will not occur. Such an evaluation is difficult but has been reported to be worthwhile.²¹

SUMMARY

Observations on a patient with salt-losing nephritis revealed the urinary concentrations of sodium, chloride, potassium, phosphorus and total solutes to be contained within narrow limits. It is suggested that tubular secretory mechanisms may have partly accounted for the fixed load. The urine flow appeared to be closely related to the sodium load. A relatively small deficit of sodium was sufficient to produce symptoms of sodium depletion.

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Observations Concerning the Origin of Shock Associated with Acute Cor Pulmonale*

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IN spite of recent progress in the field of shock, certain forms of it are not yet well understood, notably the "cardiogenic" form of shock. This appears in association with and could be due to acute failure of the heart. In a previous communication¹ the multiplicity of factors involved in cardiogenic shock was discussed. It was suggested that inadequate understanding of the mechanism of this type of shock may be due, in part, to the difficulty in observing the earliest manifestations of shock at the time when the primary and initiating factors operate, and before the secondary, sustaining factors come into play to obscure the sequence of events. The present communication deals with an instance of shock appearing during the performance of cardiac catheterization, thus providing an unusual opportunity to observe the early hemodynamic changes of shock.

CASE REPORT

L. H., a thirty-seven-year-old man, entered the hospital for evaluation and treatment of arterial hypertension. Three months prior to admission, pain in the right flank and low grade fever developed. These complaints were attributed to urinary tract infection secondary to prostatitis and were treated with prostatic massage and antibiotics. He showed an immediate favorable response to therapy, but within two months recurrences of fever and malaise occurred which were unaffected by a course of treatment with penicillin and streptomycin. He was found to have marked elevation of blood pressure and, shortly before entry to the hospital, visual disturbances, nocturia and weight loss occurred. Examination upon entering the hospital showed the systemic arterial pressure to be 215/150 mm. Hg. Advanced hypertensive retinopathy with papilledema was found on funduscopic examination. The remainder of the physical examination showed no abnormalities. Laboratory procedures revealed a normal hemogram and urinalysis. Renal

function tests and intravenous pyelograms were normal. Electrocardiogram revealed evidence of left ventricular hypertrophy. Roentgenograms of the chest showed slight tortuosity of the aorta and a slight prominence in the region of the left ventricle.

The patient was considered to have essential hypertension with early hypertensive heart disease and was treated with bed rest and hypotensive therapy consisting of oral hexamethonium salts and l-hydrazinophthalazine. His arterial pressure, which stabilized during a control period at about 180/130 mm. Hg, was reduced to an average of 160/110 mm. Hg. The patient was asymptomatic.

Three weeks after admission cardiac catheterization was performed. With the use of the conventional technique, the cardiac catheter was introduced through a right antecubital vein and guided under fluoroscopic control into the right heart and pulmonary artery. Pressure tracings were recorded by a Statham transducer and Sanborn Poly Viso recorder. Cardiac output was determined by the Fick principle with blood samples analyzed by the Van Slyke method and samples of expired air by the Scholander technic. Pressures were recorded as follows (referred to a point midway between the sternum and the table): pulmonary "wedge" pressure: 7 mm. Hg; pulmonary arterial pressure: 23/12 mm. Hg (mean 16 mm. Hg); right ventricular pressure: 24/6 mm. Hg; right atrial pressure: 7 mm. Hg. After recording pressures in the pulmonary artery and right ventricle the catheter tip was withdrawn to the right atrium. It was planned to perform serial determinations of resting cardiac output at fifteen-minute intervals while recording a continuous right atrial pressure tracing. The first determination of the cardiac output was performed one-half hour after the beginning of the procedure. The second determination of the cardiac output was made after a fifteen-minute interval. The patient was feeling well and had no difficulty in breathing into the air-collecting valve. However, a sphygmomanometric determination of the arterial pressure revealed a fall in pressure from 155/120 mm. Hg to 135/110 mm. Hg. Within ten minutes after completion of the second

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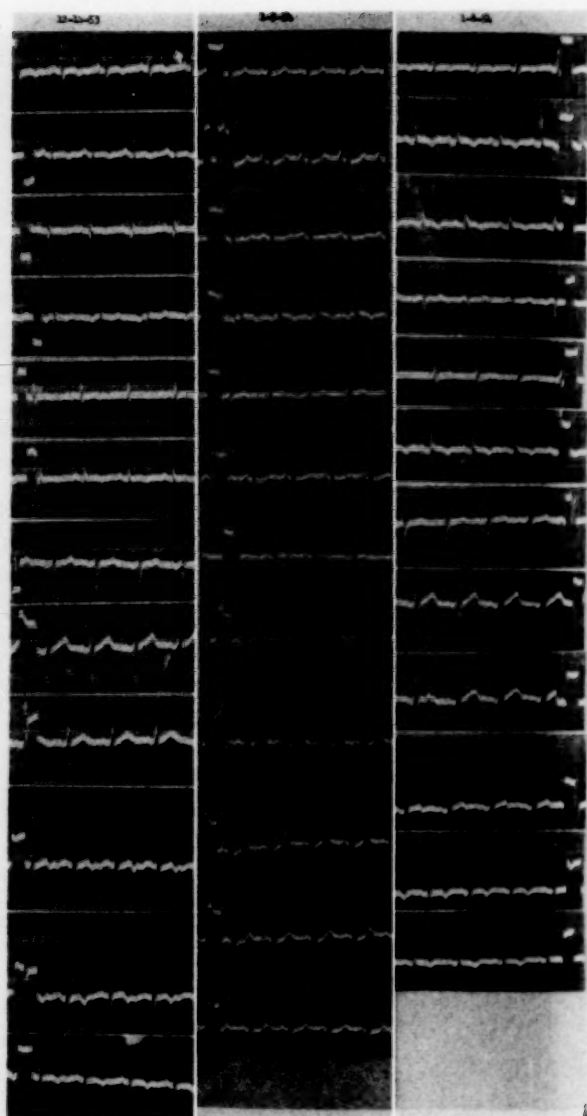


FIG. 1. Three twelve-lead electrocardiograms of patient L. H., taken shortly after admission to the hospital, one day and three days following the onset of the hypotensive episode.

cardiac output study the patient complained of "not feeling well" and a dull precordial ache developed. Gradually, the patient became restless and nauseated and had pallor and cold perspiration. The arterial pressure fell to shock levels. Cardiac catheterization was immediately terminated, the patient's feet were elevated and an infusion drip of a solution containing 8 mg. of L-norepinephrine per liter was started. The patient showed a prompt response and a normotensive blood pressure level was restored by infusing 60 to 80 drops of the L-norepinephrine solution per minute. The infusion of L-norepinephrine had to be continued for the following forty-eight hours. During this time the patient was comfortable but the dull precordial pain continued and was made worse by deep inspira-

tion. A series of laboratory studies was performed during the hypotensive episode; the electrocardiogram taken on the day following cardiac catheterization revealed a significant change. (Fig. 1.) A tall, peaked P-wave became apparent in leads 2, 3 and AVF. The electrical position changed from intermediate to semi-

TABLE 1
DATA OBTAINED FOR THE CALCULATION OF THE CARDIAC
OUTPUT DURING CARDIAC CATHETERIZATION

	First Determination	Second Determination
Total ventilation	7.6 L./min.	7.6 L./min.
Oxygen consumption	276 cc. O ₂ /min.	265 cc. O ₂ /min.
Respiratory quotient	0.77	0.77
Packed cell volume (venous)	43%	44%
Arteriovenous oxygen difference	5.2 vol. per 100 cc.	6.6 vol. per 100 cc.
Cardiac output	5.31 L./min.	4.03 L./min.

vertical; upright T-waves in lead V₁ became inverted, while all the inverted T-waves in left ventricular leads became upright. These changes persisted for a short time only, for the electrocardiogram taken two days later revealed almost complete reversal to the pre-catheterization pattern. The roentgenograms of the chest taken two days after the onset of hypotension (Fig. 2) showed a probably significant alteration. The position of the diaphragm was elevated in relation to the precatheterization film, particularly on the right side. A small amount of pleural fluid appeared in the right costophrenic angle. The size of the heart appeared larger than on the previous film, and some increase in hilar markings and pulmonary vascularity was noted, particularly on the right side. A linear density, interpreted as "disk atelectasis," was noted on the left side. These changes were thought to be consistent with, if not characteristic of pulmonary embolism. Other laboratory studies during the hypotensive period included blood and urine examinations, sedimentation rate and urinary urobilinogen determinations which were all normal.

A summary of the observations and hemodynamic determinations during cardiac catheterization is presented in Table 1 and Fig. 3. It was noted that the right atrial pressure rose gradually from 7 to 14 mm. Hg during the half-hour period of observation. At the same time the continuous electrocardiographic tracing of lead 2 showed a gradual increase in the height of the P-wave which changed its amplitude from 1 to 2 mm. The heart rate also increased slightly but significantly during this time period. The second determination of the cardiac output was significantly lower than the first one, coincidentally with the fall in arterial pressure. At the moment of the appearance of shock an abrupt change took place: the arterial pressure fell precipitously, the right atrial pressure fell and bradycardia developed.

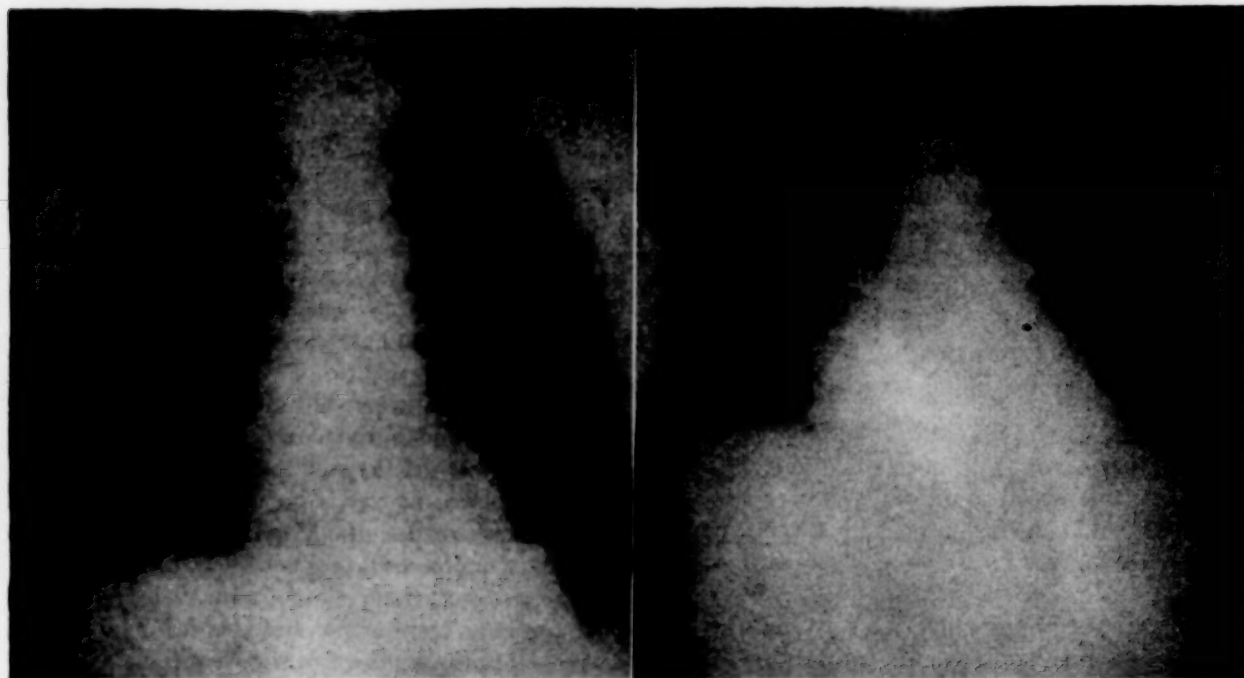


FIG. 2. Chest roentgenogram of patient L. H. before (left) and after (right) the hypotensive episode.

Following recovery from the hypotensive episode the patient made an uneventful recovery and showed a satisfactory response to therapy. When the arterial pressure became stabilized at about 160/120 mm. Hg one week after the episode, hypotensive drug therapy was restarted, reducing the arterial tension to an average of 140/105. The patient continued this regimen following discharge from the hospital but was able to reduce the dosage gradually. Some months afterwards almost normotensive levels were recorded without any hypotensive agents. A follow-up examination performed one year after the episode revealed striking regression of retinopathy and of the electrocardiographic evidence of left ventricular hypertrophy.

Comments: Three possibilities were considered as causes of the hypotensive episode in this patient: (1) simple vasomotor collapse due to pain, manipulation of the catheter and apprehension in an unusually sensitive individual; (2) shock associated with a coronary "accident"; and (3) shock associated with pulmonary embolism. Vasomotor collapse seemed unlikely on the basis of the severity and prolonged duration of hypotension. The view that shock was due to an accident within the coronary circulation would necessitate the assumption of a major myocardial infarction to explain the severity of shock. No supportive evidence for such an event has been demonstrated in the subsequent course and the serial electrocardiographic studies. On the other hand, convincing evidence is found for the occurrence of pulmonary embolism with acute cor pulmonale. Electrocardiographic findings, namely the appearance of the tall P-waves, the rotation into a

more vertical position, and the inversion of right-sided T-waves with those in left-sided leads becoming temporarily upright, strongly suggest acute right ventricular "strain," such as occurs in pulmonary embolism. Strong support for this diagnosis is found in

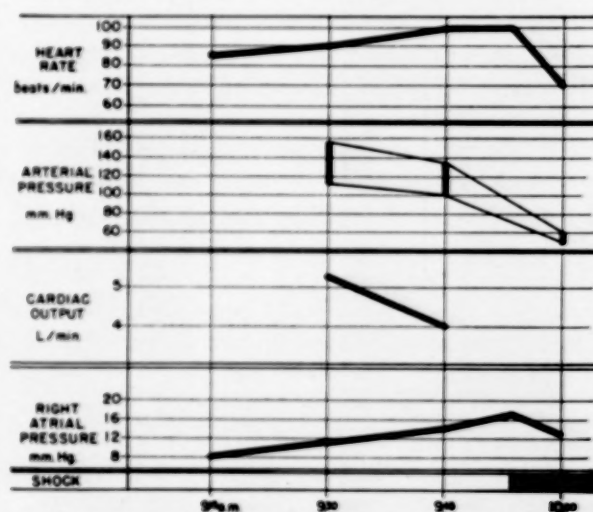


FIG. 3. Summary of hemodynamic findings observed during the early stages of the development of shock.

the roentgenographic findings and the pain in the chest.

The relationship between the cardiac catheterization study and the occurrence of pulmonary embolism is uncertain. Small pulmonary infarcts have been re-

ported as occasionally following cardiac catheterization, especially when "wedge" pressure readings were recorded. However, we were unable to find reference to a major pulmonary embolism during the procedure. Our patient had had no cardiac failure, no major cardiac enlargement and no arrhythmias. It was thought, therefore, that pulmonary embolism may have occurred fortuitously at the time of cardiac catheterization, having its origin in the leg veins and its background in the patient's inactivity and rest. However, a direct or indirect relationship between the procedure and the embolization cannot be ruled out.

COMMENTS

The term "acute cor pulmonale" is accepted to mean acute stress and failure of the right ventricle in response to a sudden increase in pulmonary vascular resistance. The resistance could be increased either by a mechanical obstruction within the pulmonary arterial tree or by constriction of pulmonary arterioles. Which of the two factors predominates in human non-fatal pulmonary embolism is not definitely established but present-day evidence favors a predominant arteriolar constriction over gross obstruction by massive embolus. Animal observations and pressure measurements in human pneumonectomies indicate that more than half of the pulmonary arterial lumen has to be obstructed or constricted in order to raise significantly the pulmonary arterial pressure. There appears to be only a narrow zone between a degree of reduction of the pulmonary arterial tree which has no important effect on the circulation and that which produces irreversible and fatal cardiac failure. Within this narrow zone an acute right ventricular strain and failure can be reproduced. If human acute cor pulmonale were caused by purely mechanical obstruction of the pulmonary arterial tree by massive embolism, then the occlusion of the lumen would have to fall within this critical zone, which is not likely to occur except in rare instances. It is therefore generally believed that acute cor pulmonale is usually caused by smaller emboli of themselves incapable of obstructing the pulmonary arterial tree significantly but reinforced by intense pulmonary arteriolar constriction leading in turn to acute right ventricular strain and failure. This mechanism is supported by experimental evidence^{2,3} for it has been demonstrated that a shower of small emboli limited to a single lobe of the lung is capable of producing severe pulmonary hypertension and right heart failure.

The hemodynamic effects of acute cor pulmonale⁴⁻⁶ are known to include an elevation of pulmonary arterial pressure, an increase in right atrial pressure and peripheral venous pressure and a fall in systemic arterial pressure. Occasionally, the systemic pressure falls to shock levels. The pathogenesis of shock associated with acute cor pulmonale is of considerable theoretic and practical importance.

In shock, the cardiac output falls abruptly, beyond the capability of the arterial system to compensate for the small flow by vasoconstriction and to maintain a tolerable systemic arterial pressure. Such a fall in cardiac output can be due to a number of factors, peripheral or central (cardiogenic). It has been postulated¹ that the concept of cardiogenic shock is justified only in reference to a situation wherein an overstretched and failing cardiac ventricle is entirely or predominantly responsible for the falling cardiac output. This is exemplified in two clinical situations: acute myocardial infarction and acute cor pulmonale. In the first instance a severely damaged left ventricle may be incapable of maintaining an adequate systemic output. In the second case the right ventricle may be overburdened by the sudden increase in resistance, with a similar result. Both of these situations can be reproduced experimentally and brief periods of shock may be observed.^{7,8} This form of cardiogenic shock in its strict sense is unquestionably operative in terminal hypotension frequently observed in patients dying of cardiac failure. It has furthermore been suspected as the underlying cause of the late, almost invariably fatal shock in the course of massive myocardial infarction. However, the pathogenesis of the commoner form of hypotension and shock appearing early in myocardial infarction and in acute cor pulmonale is a matter of controversy. This is exemplified by the conflicting recommendations for the management of such shock, whether the peripheral factors should be attacked therapeutically by the use of pressor amines^{9,10} or the central organ stimulated by cardiotonic drugs.¹¹

In this case an unusual opportunity presented itself in that circulatory studies were possible just prior to and at the point of development of shock apparently associated with acute cor pulmonale.

The hemodynamic events were observed to occur in two stages. In the first preshock stage

the patient was asymptomatic although a 25 per cent fall in cardiac output and a considerable fall in systemic pressure occurred. During this stage tachycardia developed, the right atrial pressure rose and an accentuation of the P-wave in the electrocardiogram took place, all pointing to an increase in pulmonary circulatory resistance and early right heart failure. During this stage the cardiac output fell more than the systemic pressure, indicating effective vasoconstriction and increase in systemic arteriolar resistance. The stage of clinical shock began abruptly. Coincidentally with clinical manifestations of shock a sudden fall in cardiac rate and in right atrial pressure took place. These events can best be interpreted by assuming that after the initial stage of right heart strain a peripheral factor became operative, presumably initiated by a reflex (vagal?), which led to vasodilatation, bradycardia, reduced venous return and resulted in clinical shock associated with a fall in right atrial pressure. The abrupt onset and the nature of the observed dynamic changes associated with the "shock" stage present strong evidence in favor of the neurogenic, peripheral nature of shock, and is against it being a manifestation of further right ventricular failure with "over-stretching" of the right ventricle. Such an interpretation finds further support in the response to the administration of L-norepinephrine and the favorable course.

Whether or not the mechanism described operates in other cases of shock associated with acute cor pulmonale and in cases of shock associated with acute myocardial infarction cannot be ascertained at the present time. The observations presented herewith do demonstrate, however, that in an acutely strained heart a vasodilating, shock-producing reflex may be initiated which appears to be related to the circulatory changes and not to the associated pain. This is an additional argument in favor of considering shock, associated with these two conditions, for the most part, a secondary complication rather than a direct manifestation of cardiac failure. Moreover, the rationale of directing therapeutic efforts towards the peripheral factors rather than stimulating the failing heart finds further justification.

SUMMARY

During routine cardiac catheterization of a patient, shock developed, which later was demonstrated to be due to pulmonary embolism and acute cor pulmonale. Hemodynamic studies were made during the preshock period and during the development of shock. In the earlier stage increase in pulmonary vascular resistance was indirectly demonstrated by the rise in right atrial pressure and the increase in the height of the P-wave in the electrocardiogram. During this time a moderate fall in cardiac output and a mild fall in systemic arterial pressure were observed. Onset of clinical shock was signalled by a precipitous fall in systemic arterial pressure, by abrupt fall in right atrial pressure and by bradycardia. This is interpreted as evidence of the neurogenic nature of this shock, to be considered a secondary complication of acute cardiac failure rather than a direct effect of it. The theoretic and practical implications of these observations are discussed.

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Lesions Resembling Vitamin B Complex Deficiency and Urinary Loss of Zinc Produced by Ethylenediamine Tetra-acetate*

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BECAUSE of its chelating powers ethylenediamine tetra-acetate (EDTA) is an antidote for metal poisoning.^{1,2} It has also been found to alter both *in vitro* and *in vivo* rates at which rat liver incorporates C¹⁴-tagged acetate into cholesterol and fatty acid molecules.³ To evaluate its cholesterolytic effect in man, daily injections of 1 to 12 gm. of the calcium disodium salt were given intravenously to twenty-two patients, following which circulating cholesterol fell precipitously.⁴ Mucocutaneous lesions, simulating a deficiency of vitamin B, appeared in two subjects when large total doses had been administered during a period of less than ten days.⁴ The case report of one patient follows. Because of the metal binding properties of EDTA, the renal excretion of several metals was measured during chelate therapy. The concentration of urinary zinc was found to be markedly increased. To a lesser extent iron and manganese were similarly altered; whereas copper, titanium, vanadium, molybdenum, silver, cadmium, lead and tin were not.

CASE REPORT

A forty-four year old white man was first admitted to Barnes Hospital on October 27, 1954. Five months previously, when edema of the ankles and mild exertional dyspnea had begun, albuminuria and hypoalbuminemia were found. Since early childhood spinal arthritis of the Marie-Strümpell type had been present. When the patient was twenty-five years old, migratory polyarthritis appeared briefly; at that time the first of continuing intermittent episodes of chemosis, photophobia and conjunctivitis occurred. A roentgenologic diagnosis of peptic ulceration was made in 1951; however, his minimal symptoms vanished after institution of a bland diet.

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On entering the hospital the patient weighed 70 Kg. and his vital signs were normal. Marie-Strümpell deformity, operative ankylosis of one hip joint, and generalized anasarca with pitting edema extending to the lumbar region were the significant abnormal signs. The hemogram was normal except for 21,700 leukocytes per cu. mm. of blood. The urine had a maximum specific gravity of 1.029, coarsely granular casts, and 3 to 10 gm. of protein per L. Roentgenograms of the chest revealed bilateral pleural effusion. No electrocardiographic abnormalities were noted. There were 19 mg. of non-protein nitrogen, 672 mg. of cholesterol, 2.2 gm. of albumin and 2.1 gm. of globulin per 100 ml. of plasma. Circulating electrolytes were normal. A coagulase-negative *Staphylococcus albus* was grown from the urine. Within fifteen minutes there was 30 per cent excretion of intravenously injected phenol red. The patient was given a brief course of oral hydralazine and his edema was diminished by diuretics and salt restriction. After a month in the hospital he was discharged, still exhibiting the nephrotic syndrome, with a regimen of 80 mg. of adrenocorticotrophic hormone per day plus a salt-free diet.

Because of coffee-ground vomitus and melena for several days he was readmitted on January 10, 1955. Physical signs were unchanged; however, he weighed 78 Kg. There were 16.8 gm. of hemoglobin per 100 ml. blood, but there was no leukocytosis. The only urinary changes were a decrease in the maximum specific gravity to 1.020 and the appearance of microscopic hematuria. Roentgenologic examination of the gastrointestinal tract revealed a duodenal deformity, but a guaiac test revealed no fecal blood. No electrolytic abnormalities were found. The non-protein nitrogen was 22 mg., the cholesterol 520 mg., the albumin 1.2 gm. and the globulin 1.9 gm. per 100 ml. of plasma. Amyloidosis was demonstrated by a renal punch biopsy. Three courses of EDTA proved cholesterolytic but were followed by mucocutaneous lesions or fever. After three months in the hospital, the patient

was discharged unimproved on a salt-free diet and diuretics.

The final admission was on June 17, 1955, because of extreme dyspnea and edema. The physical examination was unchanged except for tachycardia of 108 beats per minute, tachypnea of 32 breaths per minute and hepatomegaly. The patient weighed 69 Kg. The routine laboratory data were essentially unaltered except for an anemia of 12.7 gm. of hemoglobin per 100 ml. blood, a further decrease in the maximum urinary specific gravity to 1.014 and a trace of glycosuria. The electrocardiogram revealed left ventricular strain and sinus tachycardia. There were 84 mg. of non-protein nitrogen and 249 gm. of cholesterol per 100 ml. of plasma. The venous pressure measured 230 mm. of saline solution and the arm-to-tongue circulation time with decholin® was twenty-seven seconds. Digitalization and frequent thoracenteses were of no avail; the patient became increasingly azotemic and dyspneic, and died on July 6, 1955. No autopsy was permitted.

The therapy with metal binding agents deserves more detailed discussion. The cholesterolytic effect of one course of hydralazine during the first admission to Barnes Hospital and of three courses of EDTA during the second hospitalization has been reported.⁴ After a week of regular hospital food restricted as to sodium chloride, a pair of control determinations revealed 590 and 568 mg. of cholesterol per 100 ml. of plasma. Without any dietary change, 2.7 gm. of oral hydralazine was given over a period of thirteen days. On the fourth and ninth days of therapy the cholesterol concentration had decreased to 491 and 512 mgs. per 100 ml. of plasma, respectively. Neither untoward symptoms nor clinical improvement occurred. Three days after the drug was discontinued the cholesterol level was 550 mg. per 100 ml. of plasma.

There were 520 and 518 mg. of cholesterol per 100 ml. of plasma before the first course of EDTA which consisted of 2 gm. of the calcium disodium salt daily for eight days. The chelator was dissolved in 500 ml. of 5 per cent glucose in water and given over a period of at least three hours. The regular salt-free hospital diet was continued unchanged. A minimum of 412 mg. of cholesterol per 100 ml. of plasma was found on the last day of therapy; six days later the level was 656 mg. On this day a second course of EDTA was begun consisting of 3 gm. of the calcium disodium salt administered intravenously for each of seven consecutive days. No cholesterol determinations were made until four days after the chelator had again been discontinued when the concentration was reported

to be 303 mg. per 100 ml. of plasma. The third course of EDTA was begun three weeks later; its size and relation to circulating cholesterol are shown in Figure 1.

Symptoms associated with EDTA administration were initially noted on the fifth day of the

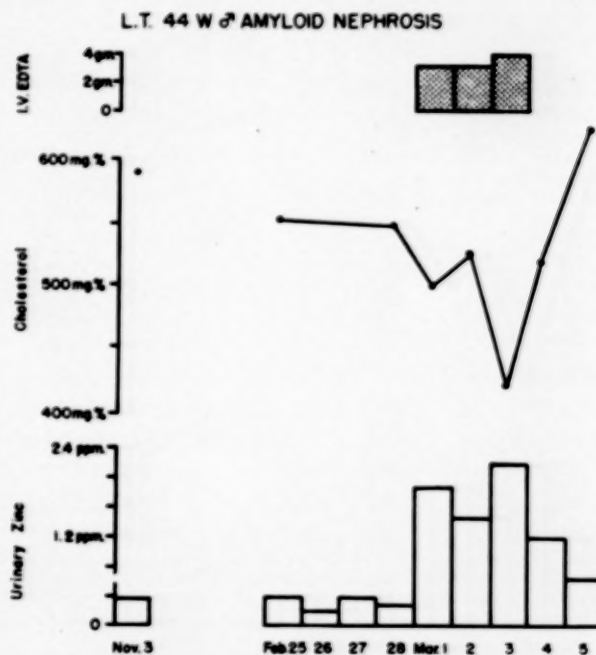


FIG. 1. Relationship between the intravenous administration of CaNa_2EDTA , the plasma cholesterol level and the concentration of zinc in the urine. The values for November 3 were obtained during the first hospitalization before hydralazine therapy.

first course which consisted of 2 gm. per day; the patient began to complain of a sore throat and cheilosis. On the sixth day his mouth and tongue were sore, and the latter was magenta in color. On the seventh day scaly, erythematous, papular lesions appeared over the face, trunk and extremities with some ulceration of contiguous mucous membranes, particularly of the nose, lips, eyes and rectum; desquamation of the scrotum was followed by a weeping serous exudation. The lesions became florid and more marked as therapy was continued for another day. Injections of EDTA were then discontinued and 10 mg. of riboflavin plus 250 mg. of nicotinamide were daily administered by mouth in addition to the 100 mg. of oral pyridoxal hydrochloride and the supplemental vitamin capsule (theragran, Squibb) that the patient had been taking for two months. The lesions rapidly subsided and healed completely in six days at which time the second series of chelate injections

TABLE I
RENAL EXCRETION OF THIRTEEN METALS

Date	CaNa ₂ EDTA Intra-venous (gm.)	Urine Volume (L.)	Urine Protein (gm./L.)	Ti	V	Cr	Mn	Ni	Zn	Mo	Ag	Cd	Pb	Sn	Fe	Cu
<i>Before, During and After Intravenous EDTA in a Nephrotic Patient</i>																
November 3, 1954	0	1.55	...	2.0	3.1	0.17	13	3.2	360	5.0	0.74	2.9	0.80	13	570	330
February 25, 1955	0	2.66	2.6	0.37	<1.0	0.14	<5.0	0.75	360	3.6	0.59	1.3	3.4	22	560	...
February 26, 1955	0	2.15	2.4	0.16	<1.0	<0.05	<5.0	1.8	170	3.5	0.76	0.88	0.28	6.0	560	162
February 27, 1955	0	1.80	2.2	0.88	<1.0	<0.05	<5.0	2.2	370	3.2	0.54	2.5	0.60	14	660	230
February 28, 1955	0	2.36	1.6	0.95	<1.0	<0.05	<5.0	2.2	240	4.1	0.57	1.4	0.22	6.4	460	265
Mean	0	2.24	2.2	0.59	<1.0	<0.07	<5.0	1.7	285	3.6	0.62	1.5	1.1	12	560	219
March 1, 1955	3	1.81	2.4	1.1	<1.0	0.11	21	2.4	1900	3.0	0.36	<0.5	0.27	2.4	1050	180
March 2, 1955	3	2.01	2.8	2.0	<1.0	0.35	12	4.0	1400	2.2	0.32	<0.5	0.07	2.2	1070	162
March 3, 1955	4	1.46	3.2	0.50	<1.0	7.3	15	16	2200	2.4	0.38	2.8	0.70	4.8	1930	187
March 4, 1955	0	1.97	2.4	0.73	<1.0	0.12	8.5	2.4	1200	1.2	0.37	4.0	0.04	3.4	1450	385
Mean	2.5	1.81	2.7	1.1	<1.0	2.0	14	6.2	1675	2.2	0.36	1.9	0.27	3.2	1375	229
March 5, 1955	0	1.73	3.2	1.3	<1.0	<0.05	<5.0	3.0	640	<0.5	0.43	3.6	0.13	3.9	...	385
<i>Renal Excretion of Thirteen Metals in Eleven Patients</i>																
Mean	0			<3.75	<0.63	<0.64	<9.7	<2.8	<66.8	14.1	0.80	<1.02	5.7	<3.22	48	9
Range	...			<0.05-10.7	<0.3-2.15	<0.05-1.0	<5-37	<0.05-12	<5-135	<0.5-13.5	0.45-1.4	<0.5-4	<0.05-13.5	<0.5-10	32-64	0-26

Note: Spectrographic analysis gave reproducible relative daily excretions, although the absolute accuracy may be lessened by the large amount of protein.

Determinations are in parts (by weight) per billion parts of urine.

consisting of 3 gm. per day was begun. On the fifth day soreness of the mouth recurred, ulceration of the buccal mucosa reappeared, and the tongue again became magenta. Two more days of EDTA administration plus high vitamin and trace metal intake (geval,[®] Lederle) with added manganese, ferrous, cobaltous, cupric and molybdate ions failed to halt the redevelopment of papular lesions. Four days after discontinuation of the chelator all symptoms had disappeared. Three weeks later, 3 gm. of EDTA were given for two consecutive days followed by 4 gm. on the next day. Nausea and vomiting with diarrhea and elevation of body temperature to 38.5°C. occurred four hours after the larger dose was begun. No more chelator was given and, despite the absence of localizing signs, leukocytosis or other laboratory evidence of infection, antibiotic therapy was initiated. Recovery was complete within a day and a half. There were no lesions of the skin or mucous membranes with this episode and none appeared during the subsequent four months of life. A febrile reaction has occurred in most patients who have received intravenously more than 3 gm. of calcium disodium EDTA in three hours.⁴

Because of the chelating properties of EDTA the renal excretion of eleven metals was followed spectrographically before, during and after administration of this agent. With precautions to prevent contamination, daily twenty-four-hour urine samples were collected beginning four days before the third course of EDTA and continuing until two days thereafter. A single similar collection was made during the first hospital admission before hydralazine was given. After all organic matter was digested, transition and nearby elements were concentrated with 8-hydroxyquinoline from 200 ml. aliquots of urine. Subsequently each sample was analyzed spectrographically in duplicate for manganese, molybdenum, lead, tin, nickel, titanium, vanadium, chromium, cadmium, silver and zinc.

Before therapy this patient's urinary excretion of the eleven elements spectrographically assayed approximated those found by us in normal individuals.⁵ There were between 250 and 300 parts of zinc by weight per billion parts of urine. According to McCance and Widdowson 0.3 mg. of zinc appeared daily in the urine⁶ while Rost found 0.6 to 1.9 mg.⁷ The urinary concentrations of the other ten metals were in

the range of one to ten parts per billion.⁵ Although the absolute concentrations given in Table I may be subject to error, the ratios of the daily levels of an element were reproducible to within 10 per cent. The most striking result of the EDTA injections was the more than sixfold increase in the excretion of zinc. A similar change in manganese levels seems to have occurred; however, the single random value during the first hospitalization approximates that following EDTA injections. The day to day variation in the urinary concentration of other elements is sufficient to obscure trends during chelate administration.

Urinary iron and copper were measured on the same specimens by chemical methods. There is obviously a significant increase in iron excretion during chelate therapy without any corresponding change for copper.

Similar but milder mucocutaneous lesions following the administration of EDTA occurred in a patient, whose case was not as well studied. This sixty-six year old white woman weighing 50 Kg., whose severe hypertension had been treated for three years with oral hexamethonium chloride, was admitted to Barnes Hospital because of increasingly severe angina pectoris. Cardiomegaly, a supine blood pressure of 200/90 mm. Hg and signs of calcific aortic stenosis were the only positive physical findings. Two multivitamin capsules (theragran), and 50 mg. pyridoxal hydrochloride orally per day were prescribed. The patient was given a test dose of EDTA consisting of 1 gm. of the calcium disodium salt intravenously and then 3 gm. for eight consecutive days. Cheilosis, chemosis, sore throat, magenta tongue and a papular rash about the shoulders appeared after 25 gm. of EDTA had been given. Her cholesterol level fell to 168 mg. from control values averaging 205 mg. per 100 ml. plasma. Her lesions rapidly vanished when EDTA was discontinued.

A normal thirty-one year old white woman who received 8 gm. of intravenous EDTA over an interval of four days without any evident ill effects also had a marked increase in the renal loss of zinc and manganese. The average pretreatment urinary concentration of these metals was 140 parts per billion of zinc and less than five of manganese. The average values during EDTA administration were 2,500 and 20 respectively. There was no effect on nickel or chromium levels which were suggestively elevated on the last day of chelate therapy in the urine

of the first patient; however, cadmium and lead excretion was increased approximately tenfold.

The fact that chelate administration increased the urinary excretion of zinc and to a lesser extent manganese and iron without significantly altering the renal loss of other trace metals assayed is surprising. The pretreatment concentrations of the trace metals which were measured spectrographically were apparently normal in this patient.⁵ As has been previously reported in nephrosis, the urinary copper and iron were greatly elevated as compared with normal values of less than ten and less than fifty parts per billion respectively.⁸ Moreover, the much greater effect of EDTA on iron than copper concentration in such a patient was also found by Cartwright, Gubler and Wintrobe.⁸ The concentration of urinary protein was very constant and no particular relationship between albumin and metal was evident. Since zinc deficiency has been reported to produce parakeratosis in pigs⁹ and in rats, with mucocutaneous lesions suggesting ariboflavinosis in the latter,¹⁰ it seems possible that the changes following chelate therapy were related to the demonstrated zinc loss. Although the lesions resembled severe avitaminosis B, particularly riboflavin or possibly pyridoxine deficiency, both patients were taking supposedly adequate oral doses of vitamins during EDTA therapy; moreover, signs and symptoms disappeared rapidly with discontinuation of chelate injections. In the nephrotic patient the syndrome reappeared after a comparable second dose. As far as is known, the sole pharmacologic action of EDTA in the human body involves chelation of trace metals. The material is stable and is apparently rapidly excreted unchanged in the urine.¹¹ It disperses through body fluids, both intracellular and extracellular.¹¹ No interference with intestinal absorption of vitamins has been demonstrated.

SUMMARY

Intravenous EDTA had a cholesterolytic effect in a hypercholesterolemic nephrotic patient. Peculiar mucocutaneous lesions resembling acute avitaminosis B occurred in this patient and in another following EDTA injections. There was a sixfold increase in the renal loss of zinc during EDTA administration as well as smaller increases in urinary iron and manganese. There was no comparable effect on cop-

per excretion or on that of nine other trace metals.

Acknowledgments: The concentration of iron was determined by Dr. Reubenia Dubach of the Department of Internal Medicine, Washington University School of Medicine, St. Louis; the concentration of copper by Dr. Clark J. Gubler of the Department of Medicine, University of Utah, Salt Lake City.

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Metal Fume Fever*

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THE purpose of this report is to bring to the attention of physicians a condition which can be readily overlooked and characterized as a "virus infection," "influenza" or "grippe," but in reality is a distinct, self-limited but disabling disease. It is a syndrome which is ignored in the standard textbooks of medicine but which can be found in texts on toxicology and industrial hygiene. It is apparently better known to plumbers than to physicians and is called "galvo" by them. However, the disease occurs also among workers in brass foundries, hence is often called brass-founders' ague and brasiers' disease. Although it is most commonly caused by zinc fumes, it apparently can be caused by other metals and is therefore called metal fume fever.

Metal fume fever is an industrial disease produced by the inhalation of zinc oxide fumes when zinc is heated in an oxidizing atmosphere to a temperature near the boiling point, as in smelting, galvanizing, brass-founding, brazing and oxyacetylene welding of galvanized iron. The symptoms are systemic, disabling and resemble those of influenza. It is characterized by chills, fever, muscular pains, nausea and vomiting, followed by some degree of prostration. Complete recovery occurs in twenty-four to forty-eight hours. Workers exposed to the disease acquire immunity to attacks but, given a period of removal from the environment as occurs following week ends or holidays, susceptibility returns.¹

CASE REPORT

A thirty-two year old white man, a plumber, was seen four hours after exposure to fumes excited by the oxyacetylene burning of galvanized pipe. He complained of malaise, generalized aches and pains in the muscles, shaking chills and fever. He also had a burning sensation in the nose and throat and a harsh dry non-productive cough. Examination revealed an acutely ill man, febrile (102°F.), his face flushed; he was extremely weak, almost to prostration. Respira-

tions were 22 per minute. Pulse rate at 110 per minute. The nasal mucosa and pharynx were reddened and moist rales were noted at both lung bases. Although breathing sounds were alveolar, pneumonia was suspected because of the symptoms and the presence of rales. At this time peripheral blood studies revealed the hemoglobin to be 16 gm. per 100 cc.; erythrocytes, 5,950,000 per cu. mm.; platelets, 200,000 per cu. mm.; leukocytes, 14,750 per cu. mm., with staff forms 4 per cent, polymorphonuclear leukocytes 78 per cent, lymphocytes 17 per cent and monocytes 1 per cent.

He was given 1,000,000 units of procaine penicillin intramuscularly. The same evening the symptoms disappeared and when he was seen the following day he was entirely symptom free and devoid of signs referable to infection in the upper respiratory tract or lungs. Nevertheless, the penicillin injection was repeated and the patient was instructed to come to the office the following day, at which time a chest x-ray was taken and proved to be entirely negative. At this time the erythrocyte sedimentation rate was 2 mm. per hour (Westergren). Repeat blood studies revealed the hemoglobin to be 15 gm. per 100 cc.; erythrocytes, 5,150,000 per cu. mm.; platelets, 250,000 per cu. mm.; leukocytes, 6,600 per cu. mm., with staff forms 0 per cent, polymorphonuclear leukocytes 76 per cent, eosinophilic leukocytes 2 per cent, lymphocytes 20 per cent and monocytes 2 per cent.

COMMENTS

The syndrome had occurred many times in this patient, at least ten, and on each occasion the symptoms were similar, although not so severe. He had never acquired immunity, since exposure to the zinc fumes was not a daily occurrence. On each occasion he was aware of exposure, and the symptoms were anticipated, unless he was fortunate enough to burn the galvanized pipe in an unconfined area. Gonzales et al.² refer to this as chronic zinc poisoning and they believe it is due to the burning of impure zinc or spelter. Sir Sidney Smith³ refers to the disease as zinc chill and says it is due to volatilized zinc. Dart^{4a} believes it is due to a foreign protein reaction similar to cotton fever in cotton

* From the Jewish Hospital of Brooklyn, Brooklyn, New York.

mill workers. Lehmann⁵ agrees and suggests that finely divided zinc fumes come in contact with the epithelial layer in the alveoli in the respiratory tract and damage the tissue protein, and subsequent absorption of the denatured protein is the cause of physiologic response, resembling a foreign protein reaction similar to that found in persons having had vaccine therapy. Schmidt-Kehl⁶ supports this theory. He observed elevation of temperature could be produced experimentally in animals by injecting blood serum that had been denatured by spraying it into a chamber containing fumes of zinc. Burstein⁷ disagrees with this theory; he believes that the effect is due to the zinc *per se* after absorption into the circulation. It is Burstein's contention that the syndrome can be induced by subcutaneous or intravenous injection of zinc salt. Lehmann⁵ injected finely powdered zinc into animals and was unable to produce the symptoms.

Although other metals may cause the symptoms,^{4b} zinc is the most common cause. This is probably because zinc has such a low boiling point (300°F.), because it has such widespread use and because zinc fumes tend to be dispersed so finely that they can penetrate the alveoli of the lungs. Larger particles of zinc oxide when inhaled do not reach the lungs but are caught and settle on the tracheal mucosa; these particles do not cause the characteristic symptoms. Sturgis et al.,⁸ report that the typical illness has been produced repeatedly in volunteer subjects who inhaled fumes of zinc or freshly burning magnesium or a suspension of finely divided heated zinc oxide, the particles of which were 0.4 microns in size. They also observed leukocytosis of 12,000 to 16,000 per cu. mm., which persisted for twelve hours after the temperature returned to normal.

It is important to note that this is a self limited disease with no complications and is not to be confused with the more dangerous form of the disease engendered by exposure to other zinc salts, namely, the fumes of zinc chloride.⁹ Evans reports ten deaths and twenty-five cases of non-fatal injury which occurred among seventy per-

sons exposed to zinc chloride fumes in a tunnel from the burning of a smoke generator. The main effects were damage to the mucous membranes of the nasopharynx and respiratory tract and a pale grey cyanosis.

SUMMARY AND CONCLUSIONS

A case is presented of metal fume fever due to zinc fumes generated by the burning of galvanized pipe by a plumber. The resemblance of this metal fume fever to severe upper respiratory infection is indicated and its short, self-limited nature is described. The temporary leukocytosis previously observed is verified and the paucity of other objective findings noted.

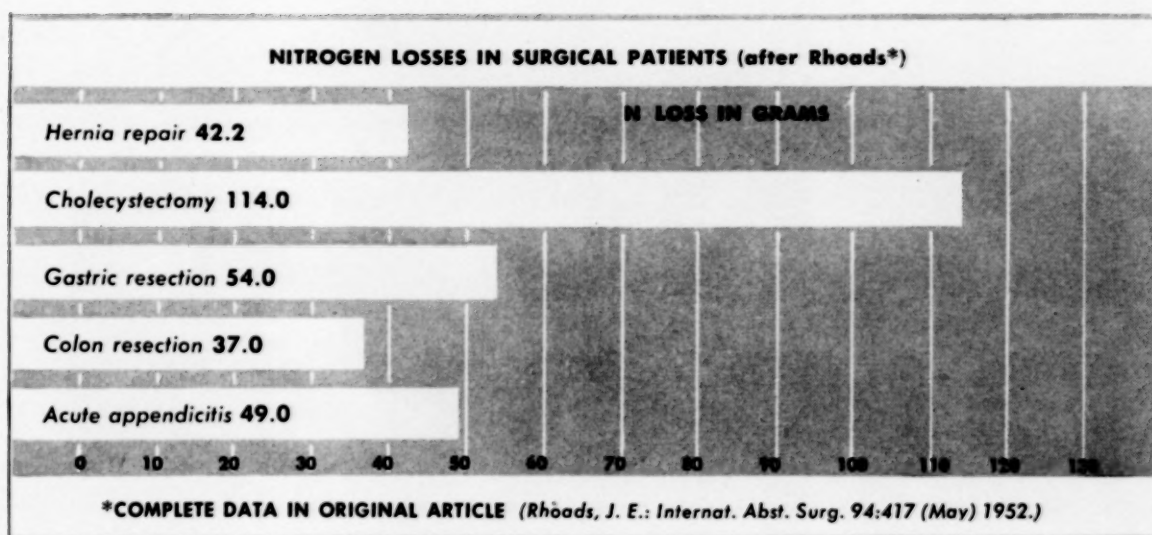
The case is reported and the extremely sparse literature on the subject discussed because knowledge of the disease is not as widespread as might be supposed.

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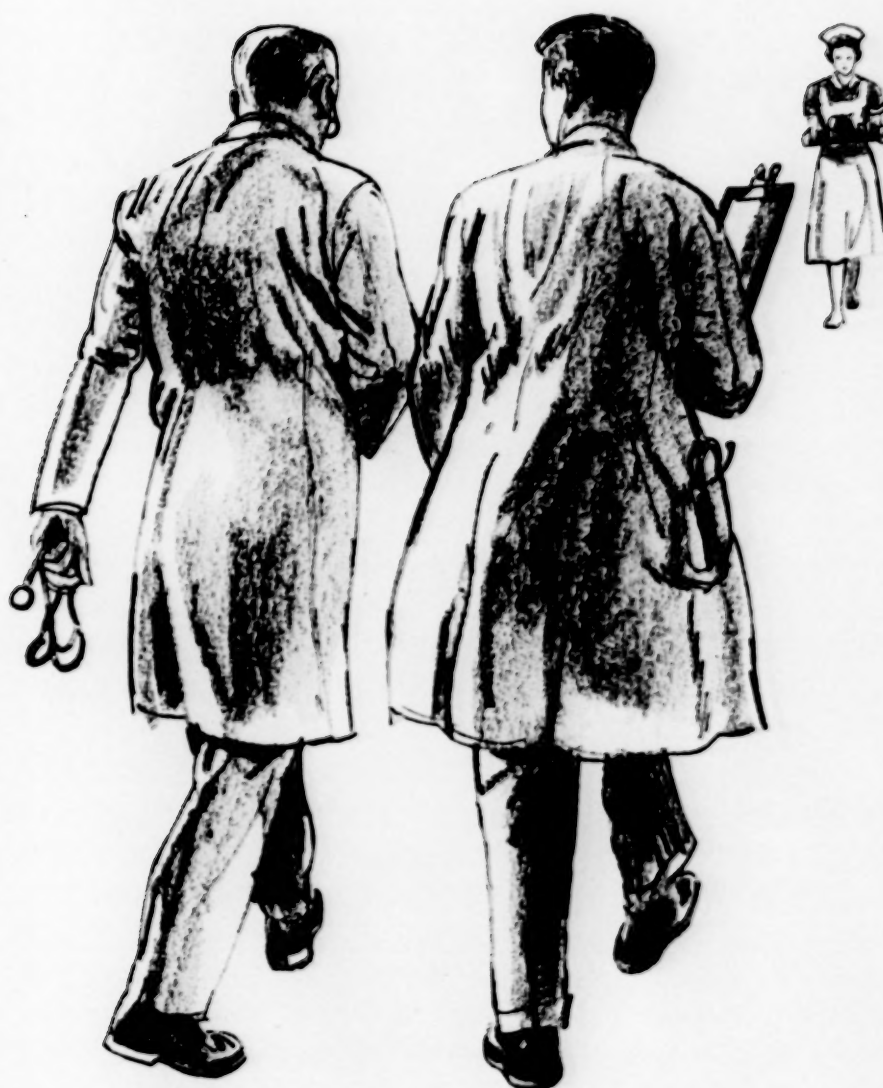
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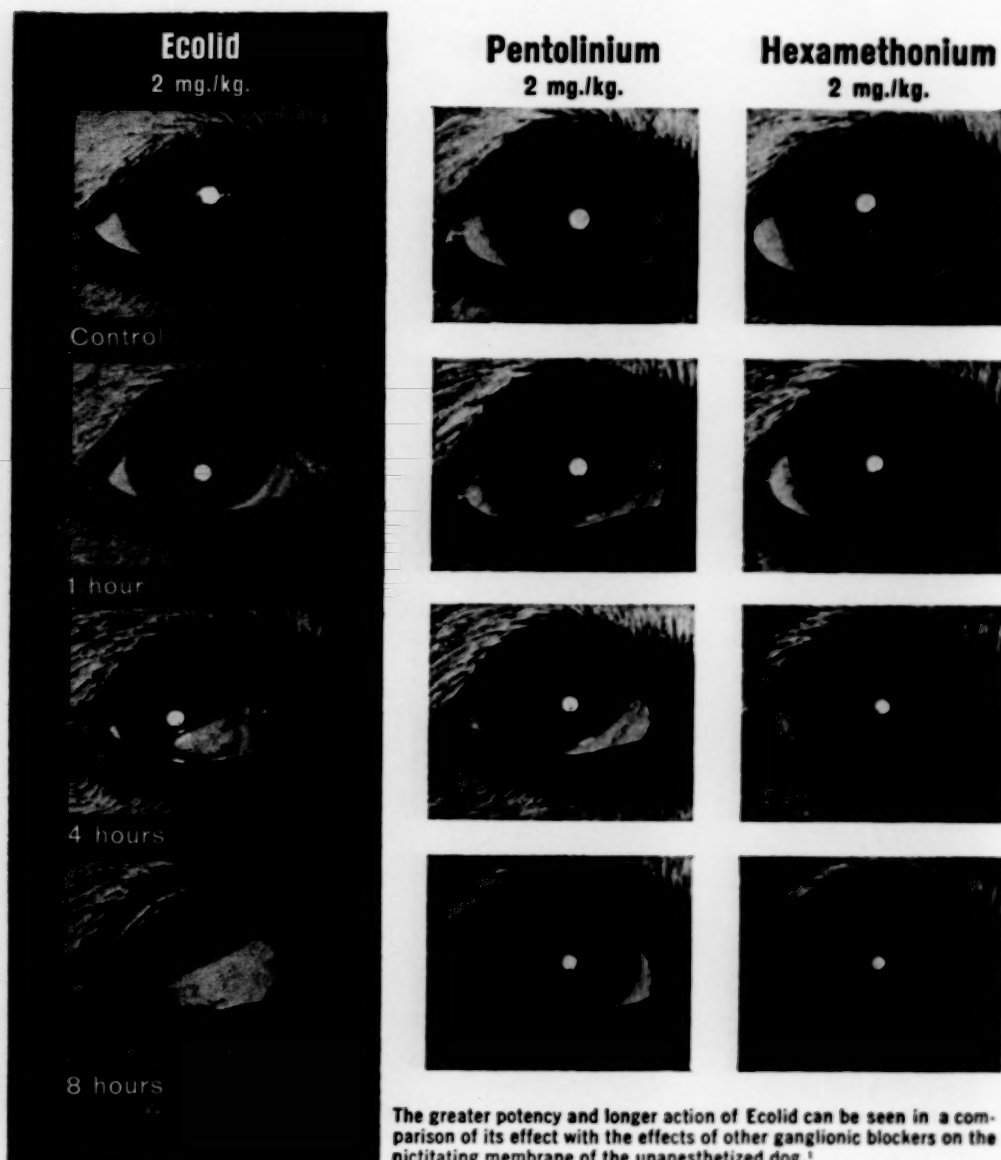
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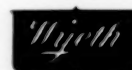
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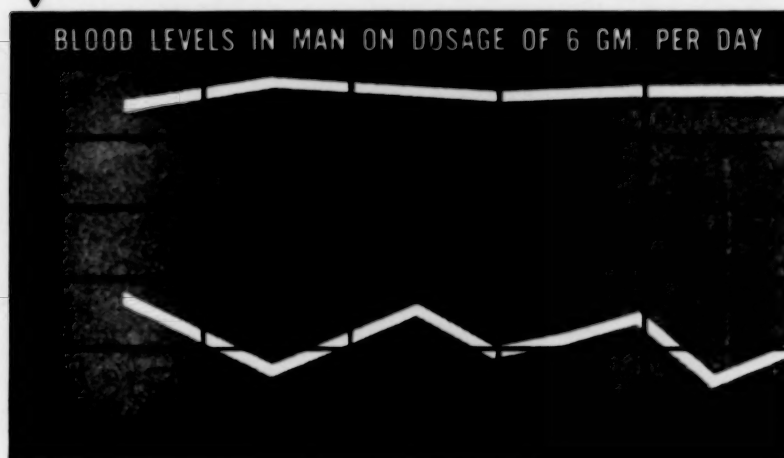
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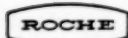
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1. Blank, P., and Boas, H.: Ann. West. Med. & Surg. 6:376, 1952.

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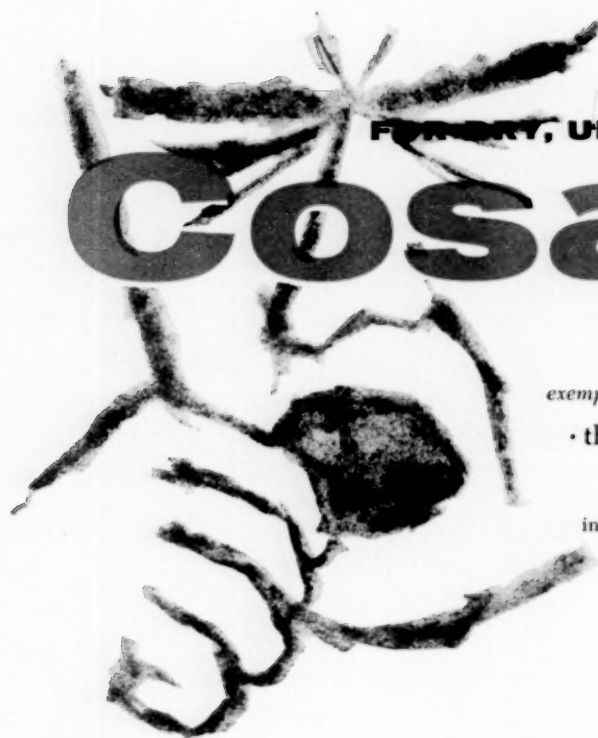
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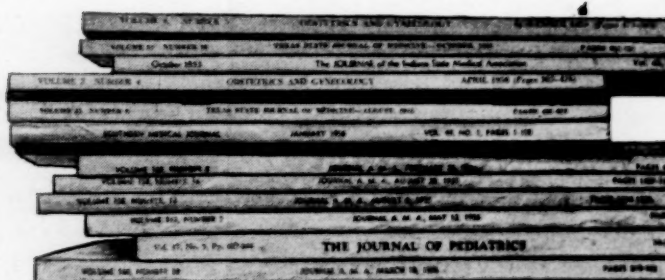
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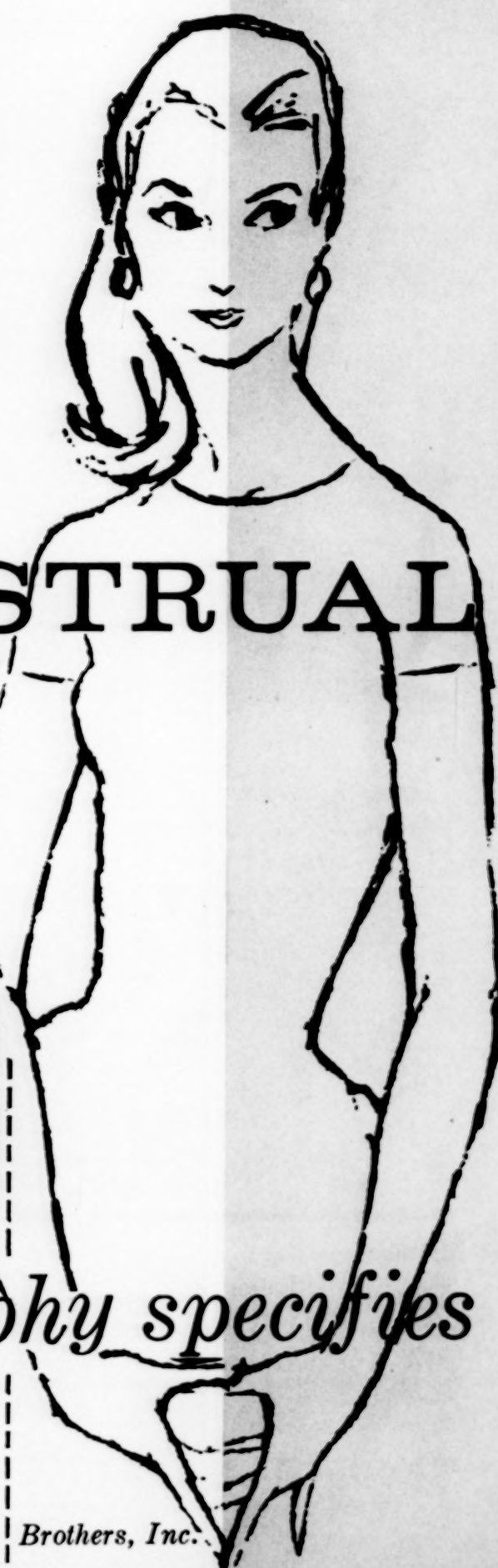
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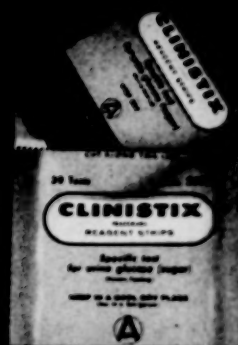
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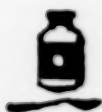
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1. Klemme, H. L.: Clin. Med., October, 1956.



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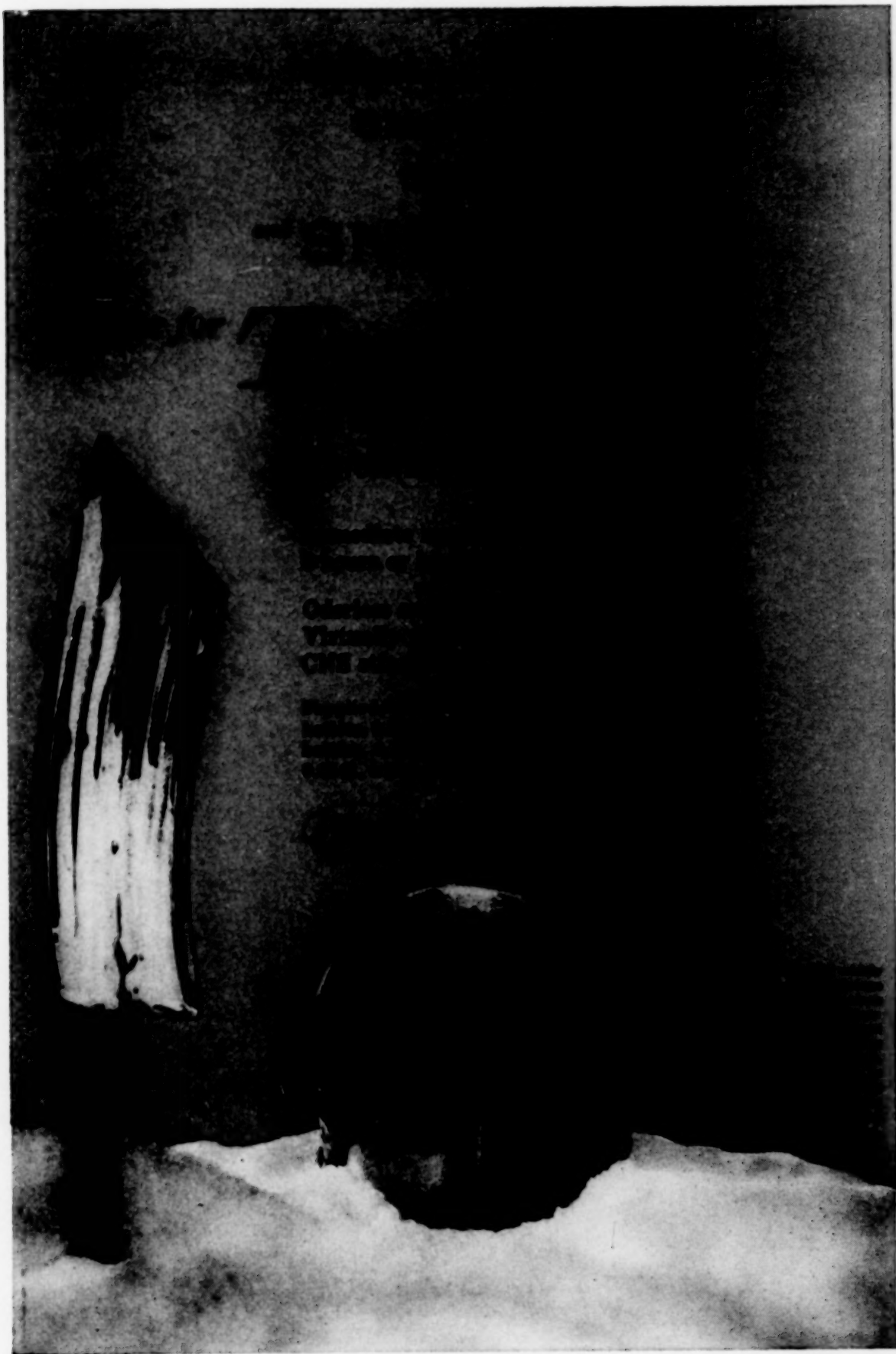
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1. Livingston, S., and Petersen, D.: *New England J. Med.* 254:327 (Feb. 16) 1956.
2. Pence, L. M.: *Texas State J. Med.* 50:290 (May) 1954.
3. Berman, B. A.: *Am. J. Psychiat.* 112:541 (Jan.) 1956.



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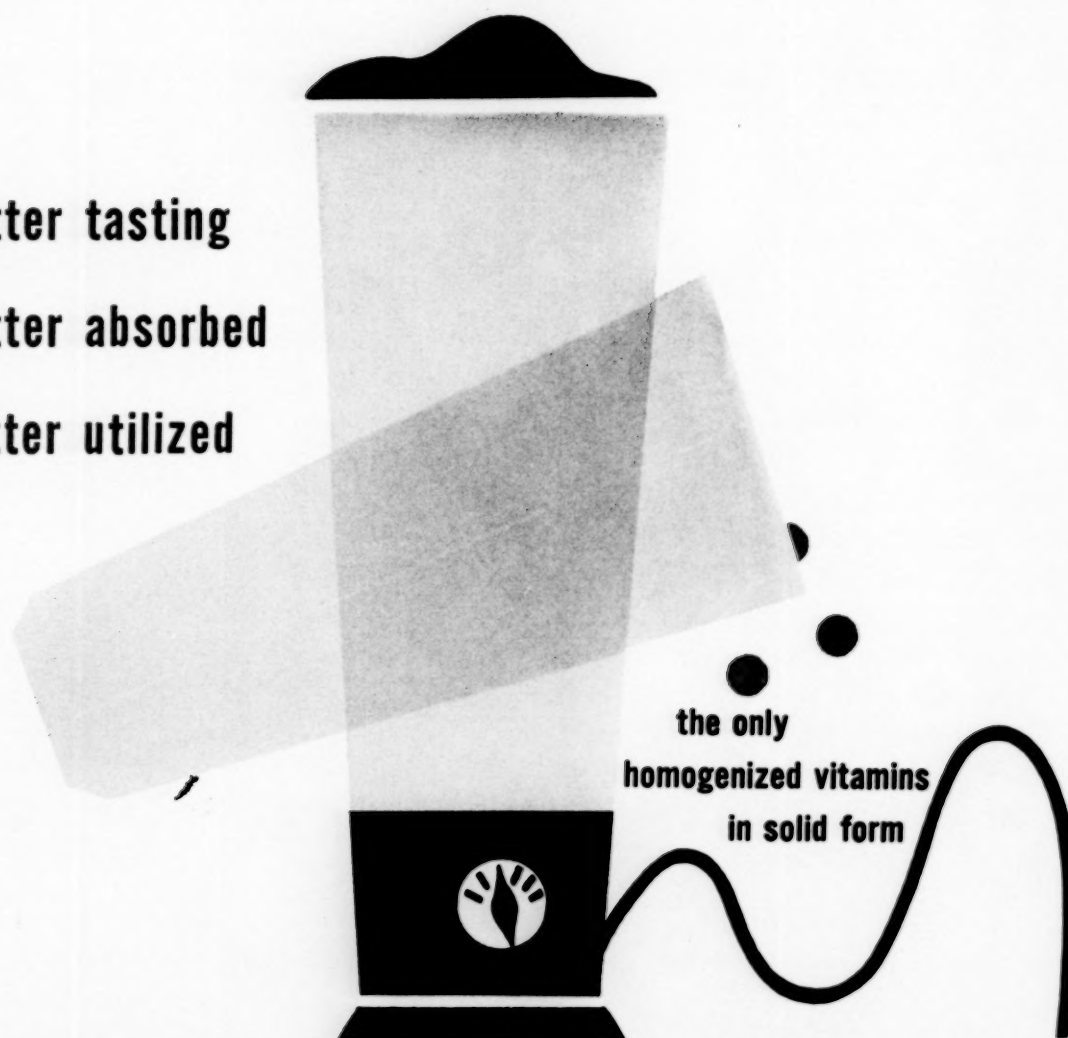
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